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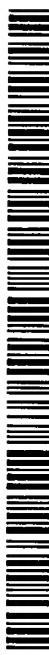
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**WO 03/013740 A1**

(54) Title: 4- AND 5-AMINO- $\alpha$ ,  $\beta$  UNSATURATED ESTER SOLID SUPPORT TEMPLATES, METHOD OF PREPARATION AND FOR USING THE SAME

(57) Abstract: A substituted  $\alpha$ ,  $\beta$ -unsaturated ester template of the general formula (1) where: P is an insoluble substrate; n is 1 or 2; X is an atom or a functional group connecting the polymer and the linker L. having a structure such as but not limited to oxygen, ester, amide, sulfur, silicon and carbon; L is a multifunctional chemical monomer in which one functional group reacts with the polymer to form a covalent bond (X) and one other of the functional groups react with one of the R groups ( $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ , or  $R_6$ ) through a plurality of chemical reactions to provide the desired templates for further chemistry. The ester template is useful for the solid phase synthesis of heterocycle compounds.

#### 4- AND 5-AMINO- $\alpha,\beta$ -UNSATURATED ESTER SOLID SUPPORT TEMPLATES, METHOD OF PREPARATION AND FOR USING THE SAME

##### Field of Invention:

The present invention relates to novel 4- and 5-amino- $\alpha,\beta$ -unsaturated ester solid support templates and methods for producing novel heterocyclic classes of compounds through a plurality of chemical  
5 reactions utilizing the solid support templates.

##### Background of Invention

Heterocyclic compounds occupy a very important position in the arsenal of clinically useful therapeutic agents. Because of the beneficial medicinal effects of members of this vast class of compounds, interest remains strong for  
10 the synthesis of novel heterocyclic compounds and known heterocyclic ring systems where there is ample novel chemistry left to explore.

Advances in molecular biology and application of automated techniques in biological screening allow the testing of a large number of compounds to be carried out rapidly and efficiently. The field of combinatorial chemistry has  
15 arisen largely out of the need to synthesize larger numbers of diverse compounds more rapidly than conventional organic synthesis techniques permit, to keep pace with high throughput biological screening capabilities. The present invention introduces a novel method based a solid support template for the efficient preparation of a wide range of novel and highly substituted  
20 heterocycles in large numbers.

Chemical synthesis of heterocyclic organic molecules on solid phase support has received considerable attention in recent years (Hermkens, P.H.H., Ottenheijm, H.C.J. and Rees, D.C., *Tetrahedron* **1997**, 53, 5643-5678; Balkenhohl, F., von dem Bussche-Hunnefeld, C., Lansky, A. and Zechel, C.,  
25 *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2288-2337; Hermkens, P.H.H., Ottenheijm, H.C.J. and Rees, D.C., *Tetrahedron* **1996**, 52, 4527-4554).

In most solid phase syntheses of heterocyclic compounds a single heterocyclic scaffold is produced where substitution from appropriate positions

on the heterocycle permits numerous analogues to be made that all possess the same heterocyclic scaffold. In order to prepare a different heterocyclic scaffold, as well as the substituents on the scaffold, requires that a new synthetic approach must be used. This oftentimes requires significant effort and time to optimize the synthetic procedure by which novel heterocyclic compounds can be prepared.

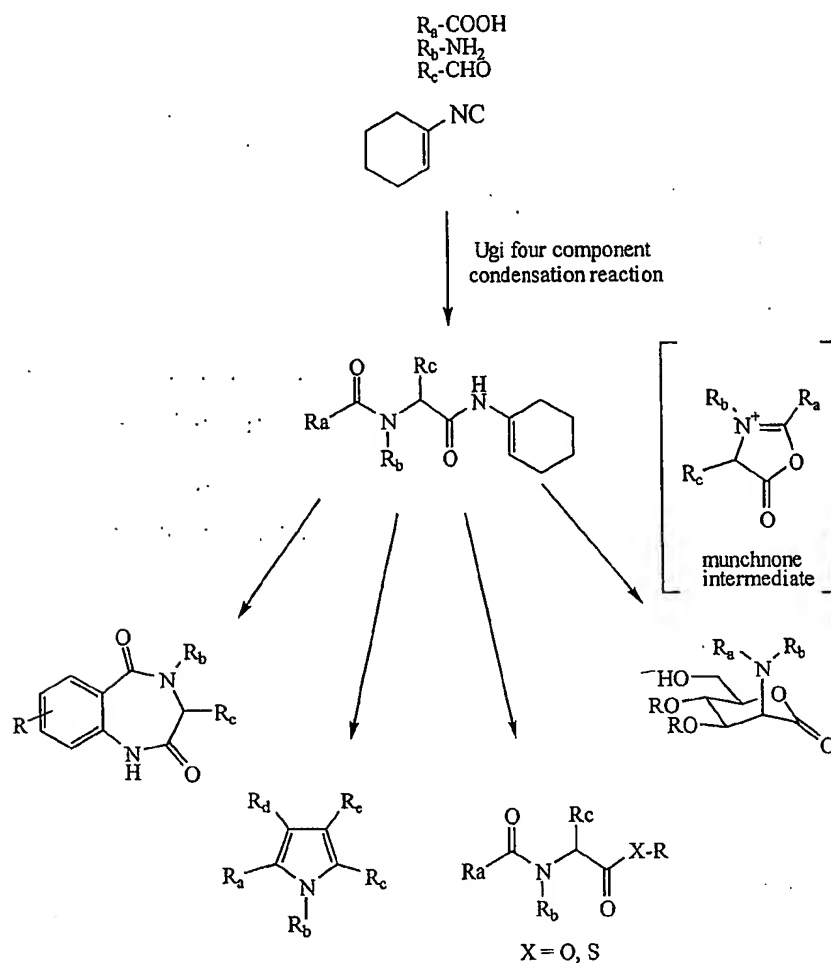
Recently published work (by Keating, T.A. and Armstrong, R.W., *J. AM. Chem. Soc.* **1996**, 118, 2574-2583) has demonstrated the synthesis of several heterocyclic & acyclic compounds from a common cyclohexenamide Ugi reaction product in solution phase (see scheme A). Chemical modification of the cyclohexenamide under acidic conditions leads to a munchnone intermediate (see scheme A) which reacts with a number of nucleophiles (alcohols and mercaptans), inter- or intramolecularly, and also dipolarophiles (disubstituted acetylenes) to form the products shown in scheme A. The synthetic strategy using the Ugi cyclohexenamide allows not only the generation of analogues of the same scaffold but also the synthesis of novel scaffolds, eg. 1,4-benzodiazepinone, pyrrole, 2-acetamido-2-deoxy-D-manno- $\delta$ -lactone and several acyclic modified Ugi products.

There is a need in the field of combinatorial chemistry for highly efficient synthetic methods like the example in scheme A for accessing a wide range of compounds that possess structural diversity in the scaffold, as well as, large numbers of analogues of single scaffolds. The synthetic method in the present invention allows the synthesis of large numbers of heterocyclic compounds on solid support where not only the side chains can be easily varied but also many unique heterocyclic scaffolds are synthesized from the same building block.

The utility of solid phase resin bound 4-aminocrotonamide for the synthesis of peptoids was recognized (Goff, D.A. and Zuckermann, R.N., *J. Org. Chem.* **1995**, 60, 5748-5749).

Since then only three other examples of the utility of the resin bound 4-aminocrotonamide have been demonstrated (Goff, D.A. and Zuckermann, R.N. *Tetrahedron Letters* **1996**, 37, 6247-6250 & Goff,

Scheme A  
Generation of Diverse Compounds Based on a Common Core

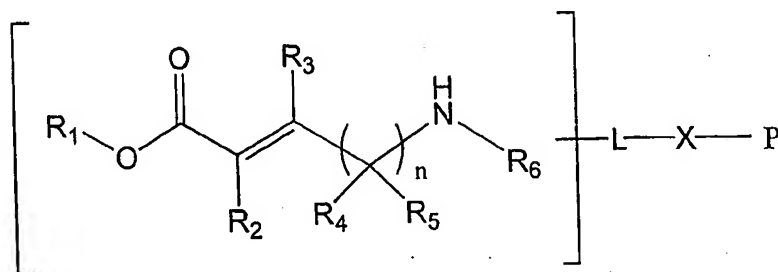


D.A., *Tetrahedron Letters* **1998**, 39, 1473-1476). Intramolecular Michael Addition on solid supported 4-aminocrotonamide led to the synthesis of 2-oxopiperazines. The synthesis of 2-imidazolidones from solid supported 4-aminocrotonamides has been recently demonstrated (Goff, D., *Tetrahedron Letters*, **1998**, 39, 1477-1480).

The present invention relates to novel 4- and 5-amino- $\alpha,\beta$ -unsaturated ester solid support templates and their use for preparing many novel heterocyclic scaffolds and analogues thereof.

Summary of Invention

The present invention relates to 4- and 5-amino- $\alpha,\beta$ -unsaturated ester solid support templates of Formula 1, wherein



Formula 1

The solid support, represented by P, is intended to include the following:

- a.) beads, pellets, disks, fibers, gels, or particles such as cellulose beads, pre-glass beads, silica gels, polypropylene beads, polyacrylamide beads, polystyrene beads that are lightly cross-linked with 1-2% divinylbenzene and optionally grafted with polyethylene glycol and optionally functionalized with amino, hydroxy, carboxy or halo groups; and
- b.) soluble supports such as low molecular weight non-cross-linked polystyrene and polyethylene glycol.

The term solid support is used interchangeably with the term resin or bead in this invention and is intended to mean the same thing.

X is an atom or a functional group connecting the polymer and the linker L, having a structure such as but not limited to oxygen, ester, amide, sulfur, silicon and carbon;

L is a suitable linker, a multifunctional chemical monomer in which one functional group reacts with the polymer to form a covalent bond (X) and the other functional groups react with one of R groups ( $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ ,  $\text{R}_5$ , or  $\text{R}_6$ ) through a plurality of chemical reactions to provide the desired templates for further chemistry. Both X and L groups can be represented within  $\text{R}_1$ , such as an amino acid. Commercially available resins, like Wang and hydroxymethyl

polystyrene, are useful in this method. The linkers present in these resins allow the cleavage of final products by a variety of mild chemical conditions that allow isolation of compounds of this invention. The hydroxymethyl polystyrene resin and the Wang resin are examples of solid phase supports used in the preparation of compounds of this invention. Other known or commercially available solid phase supports work in this method and are considered to lie within the scope of this invention.

n is 1 or 2;

One of the R groups ( $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , or  $R_6$ ) must be attached to the solid support through the linker L, it is selected from a group consisting of a covalent bond or a multifunctional chemical monomer possessing at least two attachment points which link the template backbone and the linker L. or

L and  $R_1$  are selected from a group consisting of hydrogen, alkyl, alkyl-aryl, alkenyl, alkenyl-aryl and alkylsilyl groups and substituted forms thereof;

$R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  are independently selected from a group consisting of hydrogen, substituted alkyl, substituted alkenyl, substituted alkenylaryl, substituted alkynyl, substituted aryl, substituted alkylaryl, substituted cycloalkyl and substituted alkylcycloalkyl; or

$R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  are also independently selected from a group consisting of substituted amino, substituted hydroxyl, substituted sulfhydryl, substituted alkylsulfonamido, substituted alkylcarbonylamino, substituted alkylaminocarbonylamino, substituted alkylsulfamido, substituted alkyloxycarbonylamino, substituted aryl-alkylsulfonamido, substituted arylalkylcarbonylamino, substituted aryl-alkylaminocarbonylamino, substituted arylalkylsulfamido and substituted arylalkyloxycarbonylamino; or

$R_1$  and  $R_2$ , or  $R_1$  and  $R_3$ , or  $R_1$  and  $R_4$  taken in combination, are substituted cycloalkyl and substituted saturated heterocycles;

$R_2$  and  $R_3$ , or  $R_2$  and  $R_4$ , or  $R_2$  and  $R_6$  taken in combination, are substituted cycloalkyl and substituted saturated heterocycles;

$R_3$  and  $R_4$ , or  $R_3$  and  $R_6$ , or  $R_5$  and  $R_6$  taken in combination, are substituted cycloalkyl and substituted saturated heterocycles;

### Detailed Description of the Invention

As used above, and through the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

#### 5 Definitions

"Alkyl" means a saturated aliphatic hydrocarbon group which may be straight or branched and having about 1 to about 20 carbons in the chain. Branched means that a lower alkyl group such as methyl, ethyl, or propyl is attached to a linear alkyl chain. Preferred straight or branched alkyl groups are the "lower alkyl" groups which are those alkyl groups having from 1 to about 6  
10 carbon atoms.

"Alkenyl" means an aliphatic hydrocarbon group defined the same as for "alkyl" plus at least one double bond between two carbon atoms anywhere in the hydrocarbon.

15 "Alkynyl" means an aliphatic hydrocarbon group defined the same as for "alkyl" plus at least one triple bond between two carbon atoms anywhere in the hydrocarbon.

"Aryl" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl aromatic groups covalently attached at any ring  
20 position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art. Aryl thus contains at least one ring having at least 5 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. Aryl groups may likewise be substituted with  
25 0-3 groups selected from R<sub>s</sub>. The definition of aryl includes but is not limited to phenyl, biphenyl, indenyl, fluorenyl, naphthyl (1-naphtyl, 2-naphthyl).

Heteroaryl is a group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are nitrogen, and 0-1 of which are oxygen or sulfur, said heteroaryl groups being substituted with 0-3 groups  
30 selected from R<sub>s</sub>. The definition of heteroaryl includes but is not limited to pyridyl, furyl, thiophenyl, indolyl, thiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isothiazolyl, benzothienyl, pyrazolyl, isoindolyl, isoindolyl, purinyl, carbazolyl, oxazolyl, benzthiazolyl, benzoxazolyl, quinoxaliny, quinazolinyl, and indazolyl.

"Azacycloalkane" means a saturated aliphatic ring containing a nitrogen atom. Preferred azacycloalkanes include pyrrolidine, piperidine and azepine.

"Cycloalkyl" means a saturated carbocyclic group having one or more rings and having 3 to about 10 carbon atoms. Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and decahydronaphthyl.

"heterocyclyl" means an about 4 to about 10 member monocyclic or multicyclic ring system wherein one or more of the atoms in the ring system is an element other than carbon chosen amongst nitrogen, oxygen or sulfur. The heterocyclyl may be optionally substituted by one or more alkyl group substituents. Exemplary heterocyclyl moieties include quinuclidine, pentamethylenesulfide, tetrahydropyranyl, tetrahydrothiophenyl, pyrrolidinyl or tetrahydrofuranyl.

"Carbocycles" means one or more rings having 5 to about 10 carbon atoms that possess at least one degree of unsaturation. Preferred carbocycles include cyclopentene, cyclohexene, cycloheptene, indene, di-, tetra-, and hexahydro-indene, naphthalene, and hexa- and octahydro-naphthalene.

"Saturated" means that the atom possesses the maximum number of single bonds either to hydrogen or to other atoms, eg. a carbon atom is  $sp^3$  hybridized.

"Unsaturated" means that the atom possesses less than the maximum number of single bonds either to hydrogen or to other atoms, eg. a carbon atom is  $sp^2$  or  $sp^3$  hybridized.

"Substituted" means the attachment of any of the following groups, including:

- (i)  $C_1$ - $C_6$ alkyl
- (ii)  $C_2$ - $C_6$ alkenyl
- (iii)  $C_2$ - $C_6$ alkynyl
- (iv) aryl
- (v) heteroaryl
- (vi) amino, amidino, bromo, chloro, carboxy, thiocarboxy, cyano, fluoro, guanidino, hydroxy, iodo, nitro, thiol, trihalomethyl, trihalomethoxy
- (vii) N- ( $C_1$ - $C_6$ alkyl)amidino and N-aryl amidino
- (viii) N-( $C_1$ - $C_6$ alkyl)guanidino and N-aryl guanidino



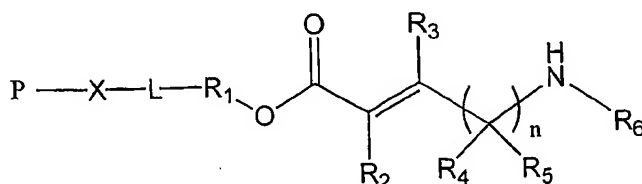
- (ix) C<sub>1</sub>-C<sub>6</sub>alkylamino and arylamino
- (x) N,N'-di(C<sub>1</sub>-C<sub>6</sub>alkyl)amino, N,N'-diaryl amino and N-(C<sub>1</sub>-C<sub>6</sub>alkyl)-N'-(aryl)-amino
- (xi) C<sub>1</sub>-C<sub>6</sub>alkylaryl amino and arylC<sub>1</sub>-C<sub>6</sub>alkyl amino
- 5 (xii) heterocyclyl
- (xiii) C<sub>1</sub>-C<sub>6</sub>alkyloxy and aryloxy
- (xiv) C<sub>1</sub>-C<sub>6</sub>alkylaryloxy and arylC<sub>1</sub>-C<sub>6</sub>alkyloxy
- (xv) C<sub>1</sub>-C<sub>6</sub>alkylarylthio and arylC<sub>1</sub>-C<sub>6</sub>alkylthio
- (xvi) C<sub>1</sub>-C<sub>6</sub>alkylcarbonyl and arylcarbonyl
- 10 (xvii) C<sub>1</sub>-C<sub>6</sub>alkylarylcarbonyl and arylC<sub>1</sub>-C<sub>6</sub>alkylcarbonyl
- (xviii) C<sub>1</sub>-C<sub>6</sub>alkoxycarbonyl and aryloxycarbonyl
- (xix) C<sub>1</sub>-C<sub>6</sub>alkylaryloxycarbonyl and arylC<sub>1</sub>-C<sub>6</sub>alkyloxycarbonyl
- (xx) C<sub>1</sub>-C<sub>6</sub>alkylarylthiocarbonyl and arylC<sub>1</sub>-C<sub>6</sub>alkylthiocarbonyl
- (xxi) N-(C<sub>1</sub>-C<sub>6</sub>alkyl) and N,N'-di-(C<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonyl
- 15 (xxii) N-(aryl) and N,N'-di-(aryl)aminocarbonyl
- (xxiii) N,N'-(C<sub>1</sub>-C<sub>6</sub>alkyl)(aryl)aminocarbonyl
- (xxiv) N-(C<sub>1</sub>-C<sub>6</sub>alkylaryl) and N,N'-di-(arylC<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonyl
- (xxv) N,N'-(C<sub>1</sub>-C<sub>6</sub>alkyl)(arylC<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonyl
- (xxvi) N,N'-(aryl)(arylC<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonyl
- 20 (xxvii) C<sub>1</sub>-C<sub>6</sub>alkylcarbonylamino and arylcarbonylamino
- (xxviii) C<sub>1</sub>-C<sub>6</sub>alkylarylcarbonylamino and arylC<sub>1</sub>-C<sub>6</sub>alkylcarbonylamino
- (xxix) C<sub>1</sub>-C<sub>6</sub>alkoxycarbonylamino and aryloxycarbonylamino
- (xxx) C<sub>1</sub>-C<sub>6</sub>alkylaryloxycarbonylamino and arylC<sub>1</sub>-C<sub>6</sub>alkyloxy-carbonyl-amino
- (xxxi) C<sub>1</sub>-C<sub>6</sub>alkylarylthiocarbonylamino and arylC<sub>1</sub>-C<sub>6</sub>alkylthio-carbonylamino
- 25 (xxxii) N-(C<sub>1</sub>-C<sub>6</sub>alkyl) and N,N'-di-(C<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonylamino
- (xxxiii) N-aryl and N,N'-diarylaminocarbonylamino
- (xxxiv) N,N'-(C<sub>1</sub>-C<sub>6</sub>alkyl)(aryl)aminocarbonylamino
- (xxxv) N-(C<sub>1</sub>-C<sub>6</sub>alkylaryl) and N,N'-di-(arylC<sub>1</sub>-C<sub>6</sub>alkyl)amino-carbonylamino
- (xxxvi) N,N'-(C<sub>1</sub>-C<sub>6</sub>alkyl)(arylC<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonylamino
- 30 (xxxvii) N,N'-(aryl)(arylC<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonylamino
- (xxxviii) C<sub>1</sub>-C<sub>6</sub>alkylcarbonyloxy and arylcarbonyloxy
- (xxxix) C<sub>1</sub>-C<sub>6</sub>alkylarylcarbonyloxy and arylC<sub>1</sub>-C<sub>6</sub>alkylcarbonyloxy
- (xl) C<sub>1</sub>-C<sub>6</sub>alkoxycarbonyloxy and aryloxycarbonyloxy
- (xli) C<sub>1</sub>-C<sub>6</sub>alkylaryloxycarbonyloxy and arylC<sub>1</sub>-C<sub>6</sub>alkyloxy-carbonyloxy

- (xlii) C<sub>1</sub>-C<sub>6</sub> alkylarylthiocarbonyloxy and arylC<sub>1</sub>-C<sub>6</sub> alkylthiocarbonyloxy
- (xliii) N-(C<sub>1</sub>-C<sub>6</sub>alkyl) and N,N'-di-(C<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonyloxy
- (xliv) N-aryl and N,N'-diarylaminocarbonyloxy
- (xlv) N,N'-(C<sub>1</sub>-C<sub>6</sub>alkyl)(aryl)aminocarbonyloxy
- 5 (xlvii) N-(C<sub>1</sub>-C<sub>6</sub>alkylaryl) and N,N'-di-(arylC<sub>1</sub>-C<sub>6</sub> alkyl)-aminocarbonyloxy
- (xlviii) N,N'-(C<sub>1</sub>-C<sub>6</sub>alkyl)(arylC<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonyloxy and  
N,N'-(aryl)(arylC<sub>1</sub>-C<sub>6</sub>alkyl)aminocarbonyloxy
- (xlix) C<sub>1</sub>-C<sub>6</sub>alkylsulfoxy and arylsulfoxy
- (l) C<sub>1</sub>-C<sub>6</sub>alkylarylsulfoxy and arylC<sub>1</sub>-C<sub>6</sub>alkylsulfoxy
- 10 (li) C<sub>1</sub>-C<sub>6</sub>alkylsulfonyl and aryl sulfonyl
- (lii) C<sub>1</sub>-C<sub>6</sub>alkylarylsulfonyl and arylC<sub>1</sub>-C<sub>6</sub>alkylsulfonyl
- (liii) C<sub>1</sub>-C<sub>6</sub>alkylsulfonamido and arylsulfonamido
- (liiii) C<sub>1</sub>-C<sub>6</sub>alkylarylsulfonamido and arylC<sub>1</sub>-C<sub>6</sub>alkylsulfonamido
- (liv) C<sub>1</sub>-C<sub>6</sub>alkylaminosulfonyl and arylaminosulfonyl
- 15 (lv) C<sub>1</sub>-C<sub>6</sub>alkylarylamino-sulfonyl and arylC<sub>1</sub>-C<sub>6</sub>alkylamino-sulfonyl
- (lvi) C<sub>1</sub>-C<sub>6</sub>alkylaminosulfonamido and arylaminosulfonamido
- (lvii) C<sub>1</sub>-C<sub>6</sub>alkylarylsulfonamido and arylC<sub>1</sub>-C<sub>6</sub>alkylsulfonamido

“Alkyl”, “alkenyl”, “alkynyl”, “aryl”, “heteroaryl” and “heterocyclyl” used for any of the groups in the above list also means substituted alkyl or substituted alkenyl, substituted alkynyl, substituted aryl, substituted heteroaryl or substituted heterocyclyl, where substituted means groups selected from the same list.

### Preferred Embodiments

A preferred solid support template of the present invention is the template of Formula 1 in which the linker L is attached to R<sub>1</sub>, can be presented as Formula 1a, wherein



Formula 1a

R<sub>1</sub> is a covalent bond, or a multifunctional chemical monomer possessing at least two attachment points which link to ester and the L;

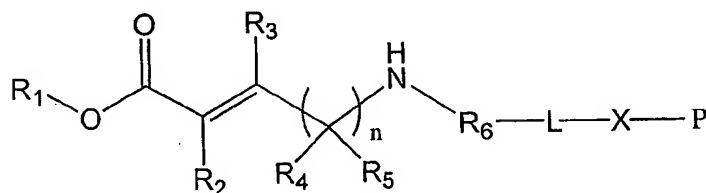
n is 1 or 2;

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from a group consisting of hydrogen, substituted amino, substituted hydroxyl, substituted alkyl, substituted alkenyl, substituted alkenylaryl, substituted alkynyl, substituted aryl, substituted alkylaryl, substituted cycloalkyl and substituted alkylcycloalkyl; or

R<sub>2</sub> and R<sub>3</sub>, or R<sub>2</sub> and R<sub>4</sub>, or R<sub>2</sub> and R<sub>6</sub> taken in combination, are substituted cycloalkyl and substituted saturated heterocyclyl; or

R<sub>3</sub> and R<sub>4</sub>, or R<sub>3</sub> and R<sub>6</sub>, or R<sub>5</sub> and R<sub>6</sub> taken in combination, are substituted cycloalkyl and substituted saturated heterocyclyl;

Another preferred solid support template of the present invention is the template of Formula 1 wherein the linker L is attached to R<sub>6</sub>, can be presented as Formula 1b, wherein



Formula 1b

R<sub>6</sub> is a covalent bond, or a multifunctional chemical monomer possessing at least two attachment points which link to "NH" and the L;

n is 1 or 2;

R<sub>1</sub> is hydrogen, substituted alkylsilyl, substituted alkyl, substituted alkenyl;

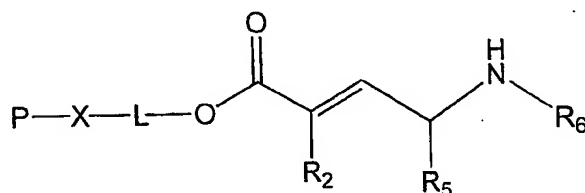
R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are independently selected from a group consisting of hydrogen, substituted amino, substituted hydroxyl, substituted alkyl, substituted alkenyl, substituted alkenylaryl; substituted alkynyl, substituted aryl, substituted alkylaryl, substituted cycloalkyl and substituted alkylcycloalkyl; or

R<sub>1</sub> and R<sub>2</sub>, or R<sub>1</sub> and R<sub>3</sub>, or R<sub>1</sub> and R<sub>4</sub> taken in combination, are substituted cycloalkyl and substituted saturated heterocyclyl; or

$R_2$  and  $R_3$ , or  $R_2$  and  $R_4$ , or  $R_2$  and  $R_6$  taken in combination, are substituted cycloalkyl and substituted saturated heterocyclyl; or

$R_3$  and  $R_4$ , or  $R_3$  and  $R_6$ , or  $R_5$  and  $R_6$  taken in combination, are substituted cycloalkyl and substituted saturated heterocyclyl;

5 Another preferred solid support template of the present invention is a template wherein the solid support P is Wang resin, Merrifield resin or other hydroxyl resins; n is 1;  $R_1$  is a covalent bond; and  $R_3$  and  $R_4$  are hydrogen. The template can be presented as Formula 1c,



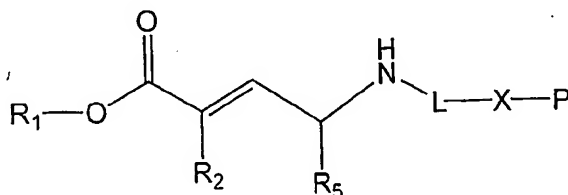
Formula 1c

10 wherein

$R_2$ ,  $R_5$ , and  $R_6$  are independently selected from a group consisting of hydrogen, substituted amino, substituted hydroxyl, substituted alkyl, substituted alkenyl, substituted alkenylaryl, substituted alkynyl, substituted aryl, substituted alkylaryl, substituted cycloalkyl and substituted alkylcycloalkyl; or

15  $R_2$  and  $R_5$ , or  $R_5$  and  $R_6$  taken in combination, are substituted cycloalkyl and substituted saturated heterocyclyl;

Another preferred solid support template of the present invention is the template of Formula 1d wherein the solid support is Rink resin, PAL resin, 20 Sieber resin or other amino resins; n is 1;  $R_6$  is a covalent bond; and  $R_3$  and  $R_4$  are hydrogen. The template can be presented as Formula 1d, wherein



Formula 1d

R<sub>1</sub> is hydrogen, substituted alkylsilyl, substituted alkyl, substituted alkenyl;

R<sub>2</sub> and R<sub>5</sub> are independently selected from a group consisting of hydrogen, substituted amino, substituted hydroxyl, substituted alkyl, substituted alkenyl, substituted alkenylaryl, substituted alkynyl, substituted aryl, substituted alkylaryl, substituted cycloalkyl and substituted alkylcycloalkyl; or

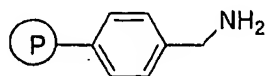
R<sub>1</sub> and R<sub>2</sub>, or R<sub>1</sub> and R<sub>5</sub>, or R<sub>2</sub> and R<sub>5</sub> taken in combination, are substituted cycloalkyl and substituted saturated heterocyclyl;

### Solid Support

Solid support is a substrate consisting of a polymer, cross-linked polymer, functionalized polymeric pin, or other insoluble material. These polymers or insoluble materials have been described in literature and are known to those who are skilled in the art of solid phase synthesis (Stewart JM, Young J.D.; Solid Phase Peptide Synthesis, 2nd Ed; Pierce Chemical Company: Rockford, Illinois, 1984). Some of them are based on polymeric organic substrates such as polyethylene, polystyrene, polypropylene, polyethylene glycol, polyacrylamide, and cellulose. Additional types of supports include composite structures such as grafted copolymers and polymeric substrates such as polyacrylamide supported within an inorganic matrix such as kieselguhr particles, silica gel, and controlled pore glass.

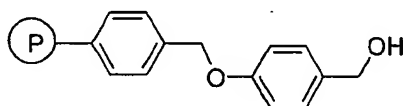
Examples of suitable support resins and linkers are given in various reviews (Barany, G.; Merrifield, R.B. "Solid Phase Peptide Synthesis", in "The Peptides - Analysis, Synthesis, Biology". Vol 2, [Gross, E. and Meienhofer, J., Eds.], Academic Press, Inc., New York, 1979, pp 1-284; Backes, B. J.; Ellman, J. A. Curr. Opin. Chem. Biol. 1997. 1, 86; James, I. W., Tetrahedron 1999, 55, 4855-4946) and in commercial catalogs (Advanced ChemTech, Louisville, KY; Novabiochem, San Diego, CA). Some examples of particularly useful functionalized resin/linker combinations that are meant to be illustrative and not limiting in scope are shown below:

- (1) Aminomethyl polystyrene resin (Mitchell, A. R., et al., J. Org. Chem., 1978, 43, 2845):



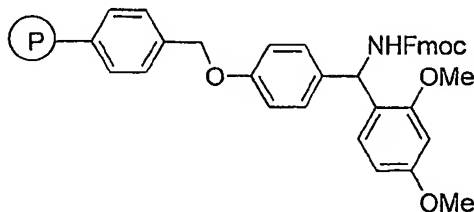
This resin is the core of a wide variety of synthesis resins. The amide linkage can be formed through the coupling of a carboxylic acid to amino group on solid support resin under standard peptide coupling conditions. The amide bond is usually stable under the cleavage conditions for most acid labile, photo labile and base labile or nucleophilic linkers.

- (2) Wang resin (Wang, S. S.; J. Am. Chem. Soc. 1973, 95, 1328-



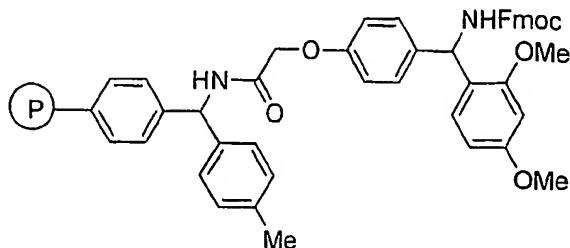
1333). Wang resin is perhaps the most widely used of all resins for acid substrates bound to the solid support resin. The linkage between the substrate and the polystyrene core is through a 4-hydroxybenzyl alcohol moiety. The linker is bound to the resin through a phenyl ether linkage and the carboxylic acid substrate is usually bound to the linker through a benzyl ester linkage. The ester linkage has good stability to a variety of reaction conditions, but can be readily cleaved under acidic conditions, such as by using 25% TFA in DCM.

- (3) Rink resin (Rink, H.; Tetrahedron Lett. 1987, 28, 3787).



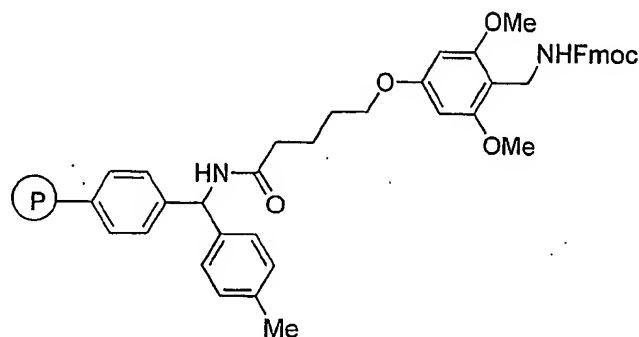
Rink resin is used to prepare amides utilizing the Fmoc strategy. It has also found tremendous utility for a wide range of solid phase organic synthesis protocols. The substrate is assembled under basic or neutral conditions, then the product is cleaved under acidic conditions, such as 10% TFA in DCM.

- (4) Knorr resin (Bernatowicz, M. S., et al. Tetrahedron Lett., 1989, 30, 4645).

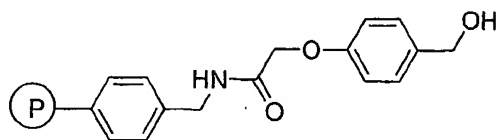


Knorr resin is very similar to Rink resin, except that the linker has been  
5 modified to be more stable to TFA.

- (5) PAL resin (Bernatowicz, M. S., et al. Tetrahedron lett., 1989, 30, 4645).

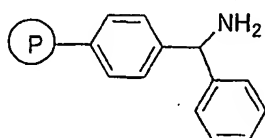


- (6) HMBA-MBHA Resin (Sheppard, R. C., et al., Int. J. Peptide Protein Res. 1982, 20, 451).

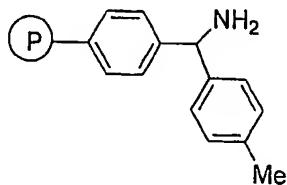


- 10 (7) HMPA resin. This also is an acid labile resin which provides an alternative to Wang resin and represented as:

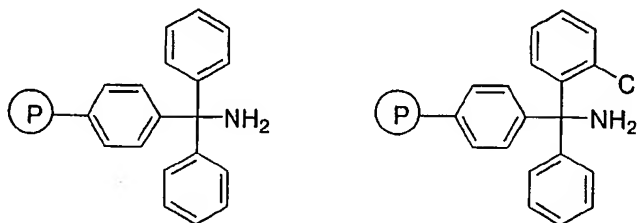
- (8) Benzhydrylamine copoly(styrene-1 or 2%-divinylbenzene) which referred to as the BHA resin (Pietta, P. G., et al., J. Org. Chem. 1974, 39, 44).



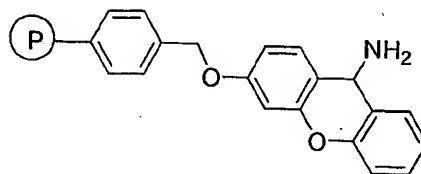
- (9) Methyl benzhydrylamine copoly(styrene-1 or 2%-divinylbenzene) which is referred to as MBHA and represented as:



- 5 (10) Trityl and functionalized Trityl resins, such as aminotrityl resin and amino-2-chlorotrityl resin (Barlos, K.; Gatos, D.; Papapholiu, G.; Schafer, W.; Wenqing, Y.; Tetrahedron Lett. 1989, 30, 3947).

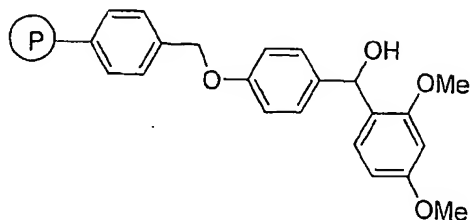


- (11) Sieber amide resin (Sieber, P.; Tetrahedron Lett. 1987, 28, 2107):



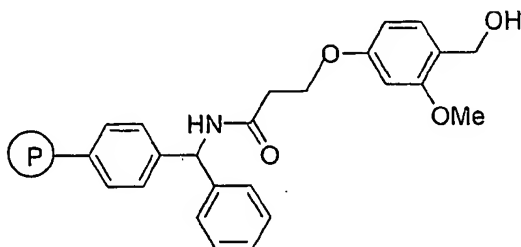
10

- (12) Rink acid resin (Rink, H., Tetrahedron Lett., 1987, 28, 3787).

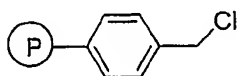




(13) HMPB-BHA resin (4-hydroxymethyl-3-methoxyphenoxybutyric acid-BHA Florsheimer, A.; Riniker, B. in "Peptides 1990; Proceedings of the 21<sup>st</sup> European Peptide Symposium", [Giralt, E. and Andreu, D. Eds.], ESCOM, Leiden, 1991, pp 131.



5 (14) Merrifield resin - Chloromethyl co-poly(styrene-1 or 2%-divinylbenzene) which can be represented as:



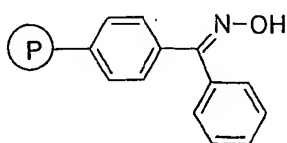
A carboxylic acid substrate is attached to the resin through nucleophilic replacement of chloride under basic conditions. The resin is usually stable under acidic conditions, but the products can be cleaved under basic and nucleophilic conditions in the presence of amine, alcohol, thiol and H<sub>2</sub>O.

10 (15) Hydroxymethyl polystyrene resin (Wang, S. S., J. Org. Chem., 1975, 40, 1235).



15 The resin is an alternative to the corresponding Merrifield resin, whereas the substrate is attached to a halomethylated resin through nucleophilic displacement of halogen on the resin, the attachment to hydroxymethylated resins is achieved by coupling of activated carboxylic acids to the hydroxy group on the resin or through Mitsunobu reactions. The products can be cleaved from the resin using a variety of nucleophiles, such as hydroxides, amines or alkoxides to give carboxylic acids, amides and esters.

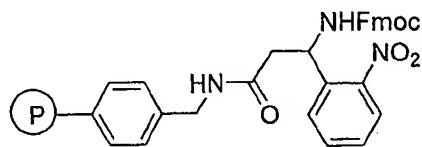
20 (16) Oxime resin (DeGrado, W.F.; Kaiser, E.T.; J.Org. Chem. 1982, 47, 3258).



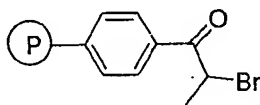
This resin is compatible to Boc chemistry. The product can be cleaved under basic conditions.

(16) Photolabile resins (e.g. Abraham, N. A. et al.; Tetrahedron Lett. 1991, 32, 577). The products can be cleaved from these resins photolytically under neutral or mild conditions, making these resins useful for preparing pH sensitive compounds. Examples of the photolabile resins include :

(a) ANP resin:

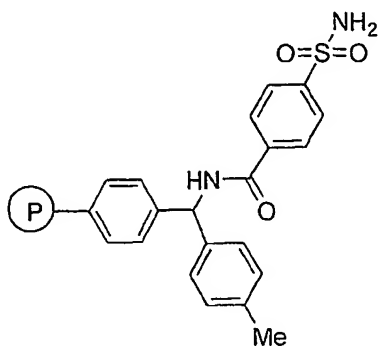


(b) alpha-bromo-alpha-methylphenacyl polystyrene resin:

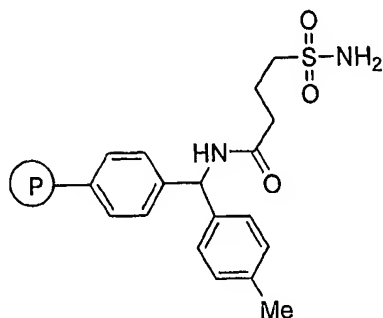


(17) Safety catch resins (see resin reviews above; Backes, B.J.; Virgilio, A.A.; Ellman, J. Am. Chem. Soc. 1996, 118, 3055-6). These resins are usually used in solid phase organic synthesis to prepare carboxylic acids and amides, which contain sulfonamide linkers stable to basic and nucleophilic reagents. Treating the resin with haloacetonitriles, diazomethane, or TMSCHN<sub>2</sub> activates the linkers to attack, releasing the attached carboxylic acid as a free acid, an amide or an ester depending on whether the nucleophile is a hydroxide, amine, or alcohol, respectively. Examples of the safety catch resins include:

(a) 4-sulfamylbenzoyl-4'-methylbenzhydrylamine resin:



(b) 4-sulfamylbutryl-4'-methylbenzhydrylamine resin:

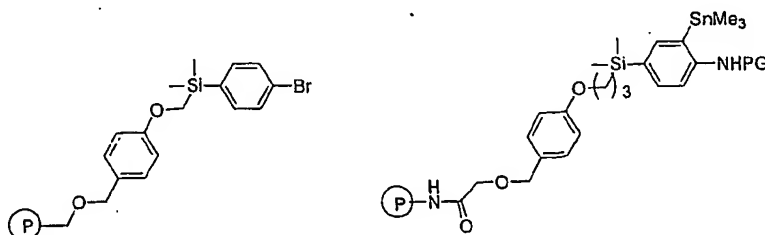


(18) TentaGel resins:



TentaGel resins are polyoxyethyleneglycol (PEG) grafted (Tentagel) resins (Rapp, W.; Zhang, L.; Habich, R.; Bayer, E. in "Peptides 1988; Proc. 20<sup>th</sup> European Peptide Symposium" [Jung, G. and Bayer, E., Eds.], Walter de Gruyter, Berlin, 1989, pp 199-201. TentaGel resins, e.g. TentaGel S Br resin can swell in a wide variety of solvents and the bead size distribution is very narrow, making these resins ideal for solid phase organic synthesis of combinatorial libraries. TentaGel S Br resin can immobilize carboxylic acids by displacing the bromine with a carboxylic acid salt. The products can be released by saponification with dilute aqueous base.

(19) Resins with silicon linkage (Chenera, B.; Finkelstein, J.A.; Veber, D.F.; J. Am. Chem. Soc. 1995, 117, 11999-12000; Woolard, F. X.; Paetsch, J.; Ellman, J. A.; J. Org. Chem. 1997, 62, 6102-3). Some examples of these resins contain protidetachable arylsilane linker and traceless silyl linker. The products can be released in the presence of fluoride.



Also useful as a solid phase support in the present invention are solubilizable resins that can be rendered insoluble during the synthesis process as solid phase supports. Although this technique is frequently referred to as "Liquid Phase Synthesis", the critical aspect for our process is the isolation of individual molecules from each other on the resin and the ability to wash away excess reagents following a reaction sequence. This also is achieved by attachment to resins that can be solubilized under certain solvent and reaction conditions and rendered insoluble for isolation of reaction products from reagents. This latter approach, (Vandersteen, A. M.; Han, H.; Janda, K. D.; Molecular Diversity, 1996, 2, 89-96.) uses high molecular weight polyethyleneglycol as a solubilizable polymeric support and such resins are also used in the present invention.

#### Preparation of the templates

According to the invention there are two general approaches to prepare the templates of the formula 1. The first approach is that the amino substituted  $\alpha,\beta$ -unsaturated carboxylic acids or their key precursors may be prepared by the conventional methods in solution phase, and then coupled to the appropriate solid support to afford the solid support templates of formula 1 as shown in **Schemes 1-3**. These compounds or their precursors may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature. The second approach is that the core structures of 4- and 5-amino- $\alpha,\beta$ -unsaturated ester templates are constructed on solid support as shown in **Schemes 4-6**.

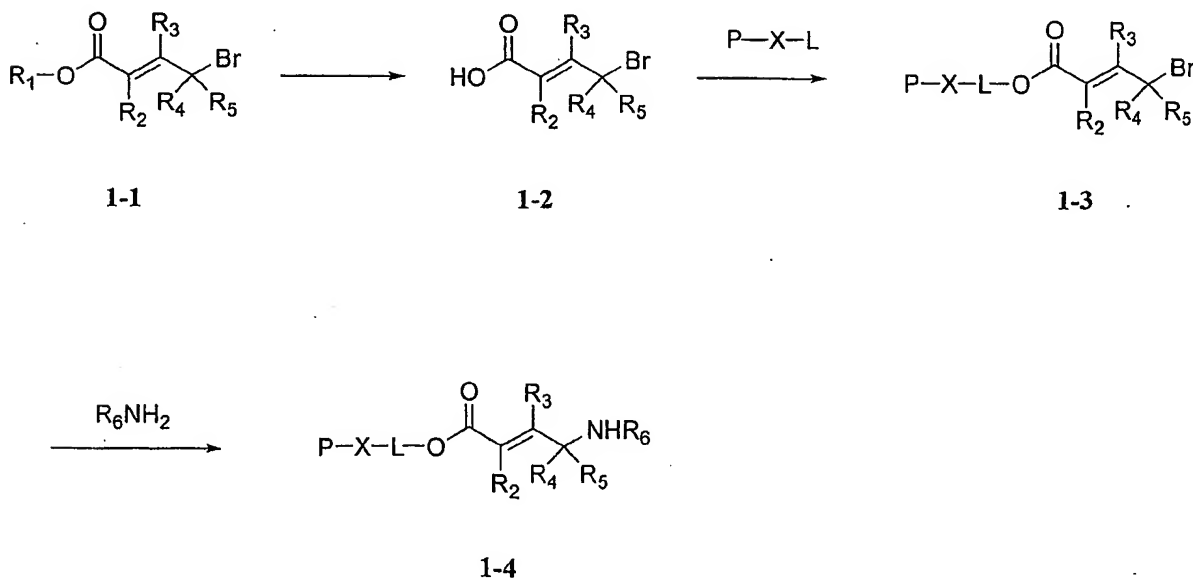
General methods for preparing templates according to the invention may be prepared as described in the schemes as follows.

**Scheme 1** refers to the preparation of 4-amino- $\alpha,\beta$ -unsaturated ester (4-aminocrotonate) templates from the corresponding 4-bromocrotonate compounds. Hydrolysis of a compound of formula 1-1 is carried out under very mild conditions in the presence of base, such as LiOH, gives a free carboxylic acid of formula 1-2. A subsequent coupling to the solid support, such as Wang resin and hydroxymethyl resin, is achieved by applying the Mitsunobu method (Diakyl azacarboxylate, PPh<sub>3</sub>) to give a bromocrotonate solid support template of formula 1-3. From this core intermediate the desired 4-aminocrotonate

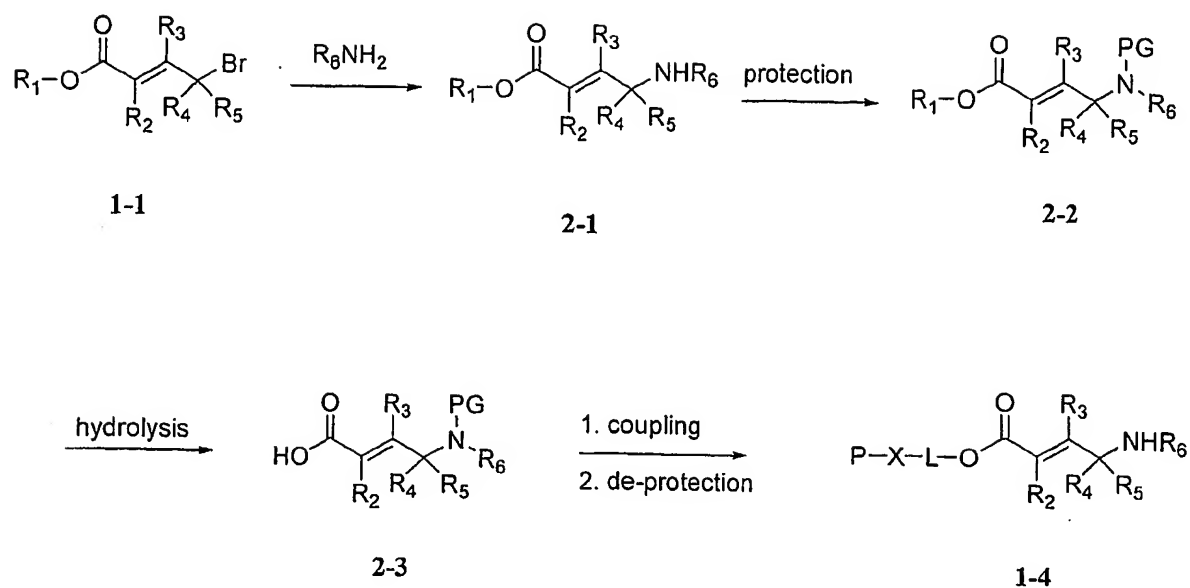
template can be readily obtained by the treatment with appropriate amines in solvent, such as DMF, NMP etc.

The amine displacement may also be achieved in solution phase as described in **Scheme 2**. Protection of amino functional group followed by hydrolysis results in a free carboxylic acid of formula 2-3 which is then coupled to the solid support under appropriate conditions, such as Diaklyl azacarboxylate /PPh<sub>3</sub>, DIC/DMAP, EDC/DMAP, etc. De-protection gives the desired template of formula 1-4.

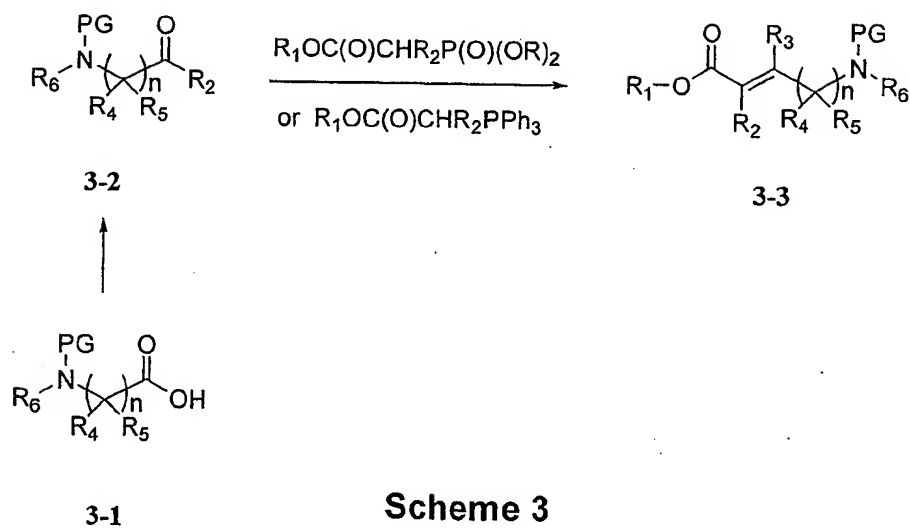
**Scheme 3** illustrates an alternative means for the preparation of 4- or 5-amino- $\alpha,\beta$ -unsaturated ester. An  $\alpha$ - or  $\beta$ -amino acid derivative can be readily converted into the corresponding aminoketone or aminoaldehyde by using conventional method known in the art, such as J. Org. Chem., 56, 2624 (1991); 59, 1796 (1994); 60, 8118 (1995); and Tetrahedron Lett., 31, 5689 (1990). The double bond can be then formed via Wittig or Horner Emmons reaction by using an appropriate ylid under standard conditions known in the art, as described in J. Chem. Soc. Chem. Commun. 1605 (1995) and J. Org. Chem., 56, 5729 (1991), to give a key intermediate of formula 3-3.



**Scheme 1**



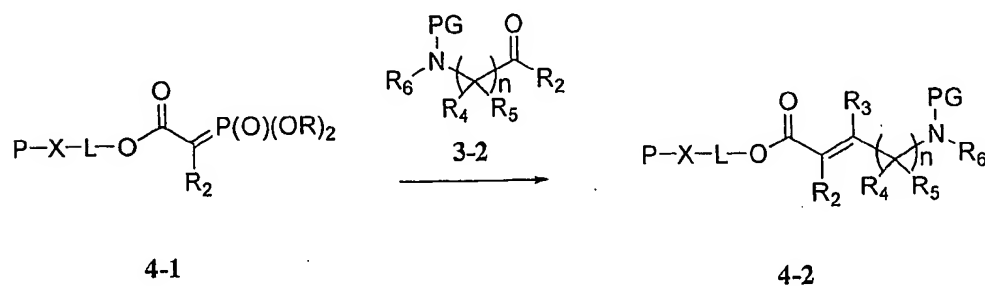
Scheme 2



Scheme 3

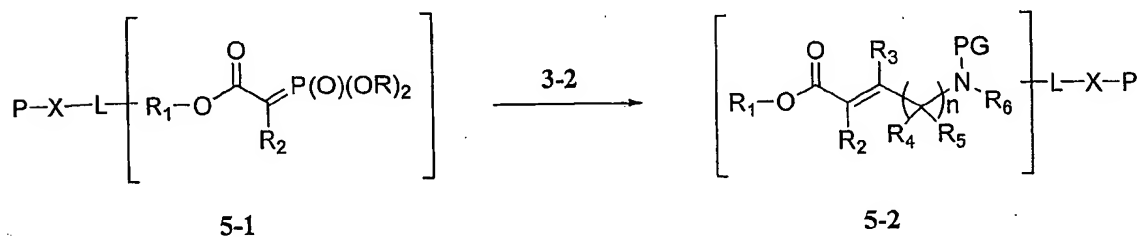
The Wittig or Horner Emmons reaction may be carried out on solid

support as described in **Schemes 4-6**. **Scheme 4** illustrated below, refers to a polymer-bound phosphonate of formula 4-1 which reacts with an N-protected aminoketone or aminoaldehyde under basic conditions, such as LHMDs/THF, to construct the template directly on solid support. The approach may also be applied to a solid support phosphonate linking to the solid support via R<sub>1</sub> or R<sub>2</sub>



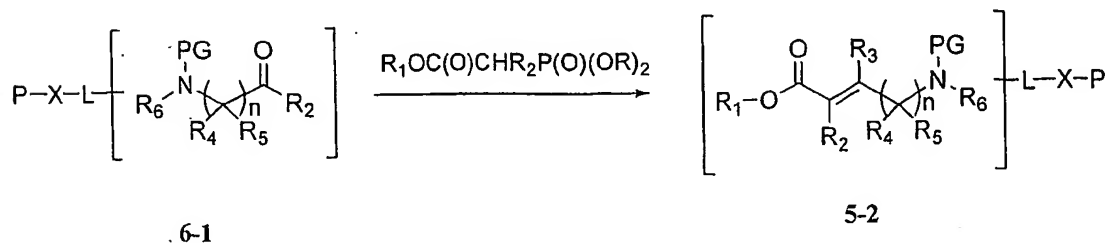
#### Scheme 4

as shown in **Scheme 5**. Alternatively, the direct assembly of the templates on solid support may be achieved by using a polymer-bound aminoketone or aminoaldehyde reacting with the corresponding ylid as described in **Scheme 6**.



Formula 1

#### Scheme 5



#### Scheme 6

### Synthesis of novel heterocycle scaffolds using the templates

The schemes 7 – 12 illustrate the synthesis of novel heterocycle scaffolds on solid support utilizing the 4- and 5-amino- $\alpha,\beta$ -unsaturated ester templates of formula 1 in the present invention.

5 Standard amide bond reaction conditions are used to couple carboxylic acid intermediates, eg. **7-1**, to the 4- and 5-amino- $\alpha,\beta$ -unsaturated ester-linked solid support template of Formula 1. Several examples of amide bond forming reaction conditions are diisopropylcarbodiimide (DIC), hydroxybenzotriazole and DMF, 10-24 h, room temperature; 1- (3-dimethylaminopropyl) -3-ethylcarbodiimide hydrochloride (EDC), DMF, 1-24hrs, room temperature; and 10 bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP), diisopropylethylamine, dichloromethane, 1-24 hrs, room temperature. Other reaction conditions known to those skilled in the art of forming amide bonds from carboxylic acids and amines are considered to lie within the scope of this 15 invention.

The Ugi four-component condensation is utilized in this method, where the amine component of the reaction is the solid support bound 4- or 5-amino- $\alpha,\beta$ -unsaturated ester. Utilization of this reaction in this way allows for the incorporation of diversity in the heterocyclic scaffold generation by the choice of 20 the carboxylic acid component. The substituents on E (where E =  $\text{CHR}_8\text{-CO-NHR}_9$ ) are controlled by the choice of the aldehyde,  $\text{R}_8\text{-CHO}$  and the isocyanide,  $\text{R}_9\text{-NC}$ .

Orthogonal protecting group strategies utilized in this approach are known in the art and allow chemical manipulation of multi-functionalized 25 intermediates in solution or solid phase chemistry. A single protecting group like a t-butyloxycarbonyl (Boc)-protected amine can be removed under acidic conditions, eg. Trifluoroacetic acid in dichloromethane, without removing another protecting group, like a 9-fluorenylmethyloxycarbonyl (Fmoc)-protected amine. Altering the protecting group removal conditions such that treatment of 30 an Fmoc- and Boc-bis-protected diamine like the formation of a solid support bound intermediate **10-1** with base, eg. 20% piperidine in DMF, selectively removes the Fmoc-protecting group to liberate the free amine. In this way, very high chemoselective control is achieved and side product formation is



minimized. Other known protecting groups are considered within the scope of this invention.

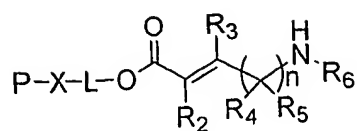
Heterocyclic ring formation occurs at several stages of this method. Fmoc-protecting group removal from an amine liberates the free amine that  
5 undergoes intramolecular Michael reaction (conjugate addition) with the  $\alpha,\beta$ -unsaturated crotonate-linked resin, eg. see conversion of solid support bound **7-2** to **7-3**, or **8-1** to **8-2**, or **9-1** to **9-2**, or **11-2** to **11-3**, and other examples within this invention. Cyclization also occurs in this method by intramolecular reaction of an internal nucleophilic heteroatom (eg. an amine, alcohol or  
10 mercaptan) with the crotonate carbonyl thus forming a product heterocycle. Some examples of this conversion are solid support bound **9-3** converted to **12-1** and **12-2** shown in **Scheme 12**. Acid, or base, and/or heat sometimes catalyze this cyclization.

Other heterocyclic ring forming reactions of this method are the  
15 formation of ketopiperazine, imidazolidine, oxazolidine and thiazolidine rings from diamine, aminoalcohols and aminomercaptans, respectively, by intramolecular cyclization followed by coupling with alpha-bromoacetic acid or condensation with aldehydes as exemplified by conversion of **10-5** to **10-6**, or **10-2** to **10-3**. Imidazole formation is performed by an intramolecular  
20 condensation of an  $\alpha$ -amidoketone with ammonium acetate in hot (95-100°C) acetic acid for 10-24 hours as exemplified by the conversion of **11-1** to **11-2**.

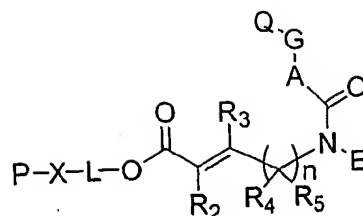
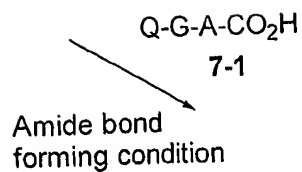
Amines, which are liberated at many stages of the syntheses in this method, are reacted with electrophilic reagents including acid halides, acid anhydrides, isocyanates, sulfonyl halides, alkyl halides,  $\alpha$ -halo-carboxylic  
25 acids, esters or ketones, activated protected amino acids and other electrophiles. The use of these chemical inputs (reagents or raw materials) allows large numbers of structurally diverse analogues to be prepared and also leads to intermediates that by further manipulation lead to novel heterocyclic structures, eg. conversion of **7-3** to **7-4**, or **9-2** to **9-3**, or **10-5** to **10-6**, or **11-3**  
30 to **11-4**, or **12-1** and **12-2** via intermediate **9-3**.

Cleavage of compounds from solid support depends on the nature of the solid support used in the synthesis. The react and release strategy can be performed on a Merrifield (hydroxymethyl polystyrene resin), Wang resin, Hydroxymethylbenzoic (HMBA) acid resin and Hydroxymethylphenoxy

functionalized Tentagel resin to name a few. Cleavage of compounds under mild acidic conditions like trifluoroacetic acid (20-95%) is done with Benzhydrylamine or Rink type resins and Wang resins among others. Cleavage of substrates from solid support by reaction with nucleophiles like ammonia, methylamine, hydroxylamine, methanol and triethylamine is done from Hydroxymethylpolystyrene and HMBA resins to give compounds as their carboxamides, hydroxamic acids and methyl esters. Cyclative cleavage occurs in this method by intramolecular reaction of an internal nucleophilic heteroatom (eg. an amine, alcohol or mercaptan) with the crotonate carbonyl attached to the solid support, thus forming a product heterocycle and simultaneously releasing the compound from the solid support (react and release strategy). Other known or commercially available resins are considered within the scope of this invention.



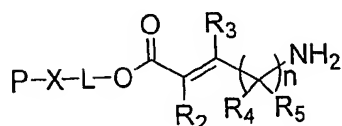
Formula 1a  
R<sub>1</sub> is covalent bond



7-2

G = NR<sub>18</sub>, Q = protecting group  
G = S or O, Q = Hydrogen

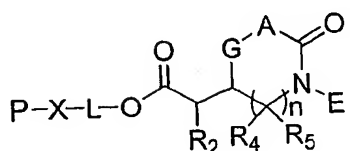
Ugi conditions results in  
E = CHR<sub>8</sub>-CO-NHR<sub>9</sub>



Formula 1a  
R<sub>1</sub> is covalent bond  
R<sub>6</sub> is hydrogen

Ugi 4-components  
condition:  
carboxylic acid 7-1  
R<sub>8</sub>-CHO  
R<sub>9</sub>-NC

De-protection  
followed by  
conjugate addition

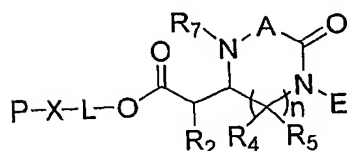


G = NR<sub>18</sub>, S, O

7-3

electrophilic reagents,  
eg., isocyanates  
acid chloride,  
sulphonyl chloride

G = NH



7-4

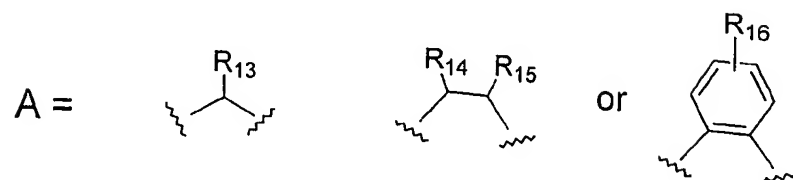
R<sub>7</sub> = -C(O)NHR<sub>10</sub>  
-C(O)R<sub>11</sub>  
-S(O)<sub>2</sub>R<sub>12</sub>

Scheme 7

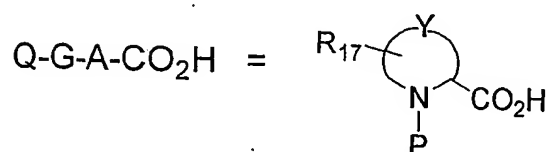
Definition of Q-G-A-CO<sub>2</sub>H, 7-1:

Q is an appropriate protecting group,

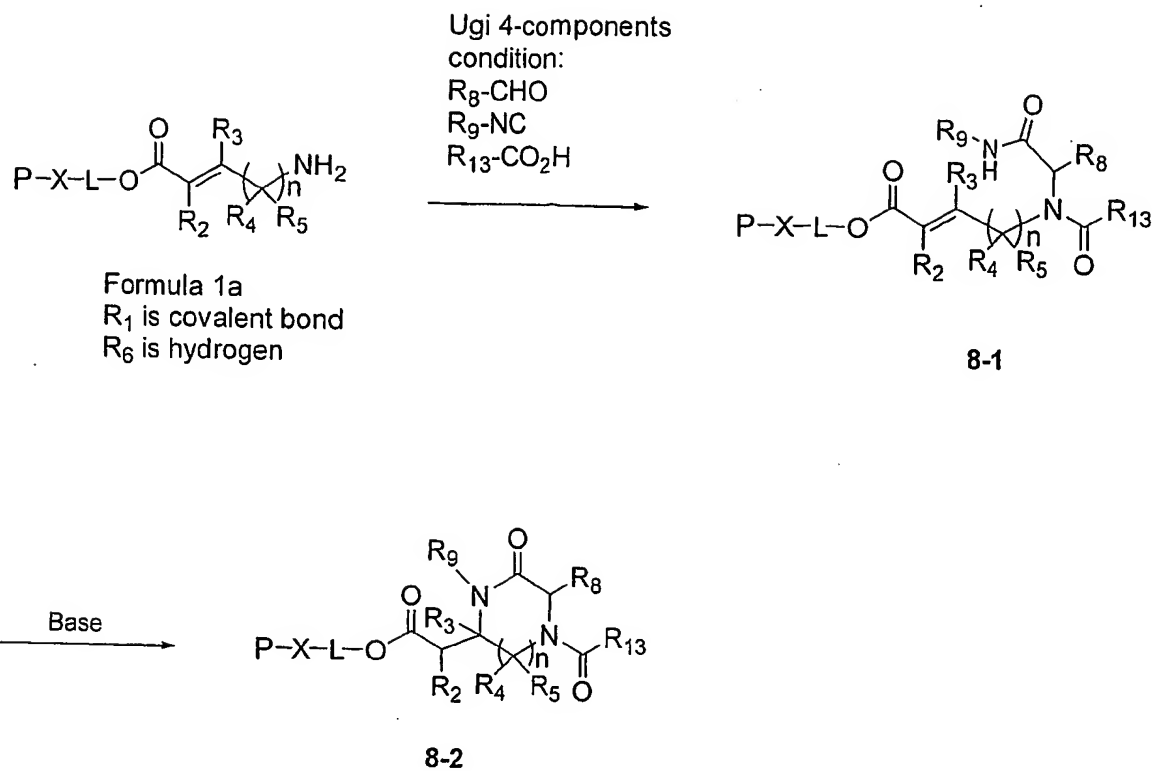
G is NR<sub>18</sub>, S or O,



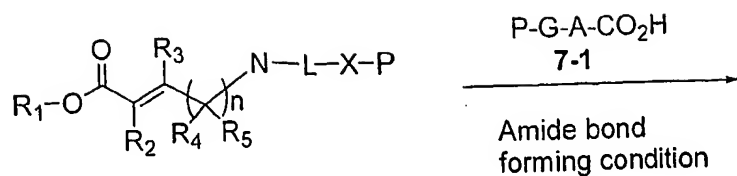
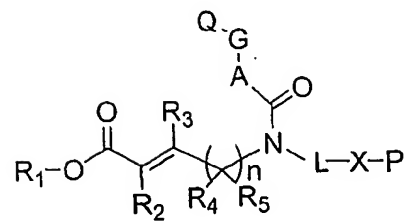
or



**Scheme 7 Continued**

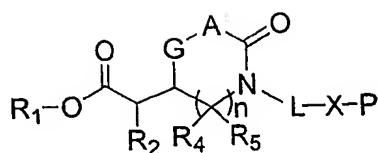


Scheme 8

**Formula 1b****9-1**

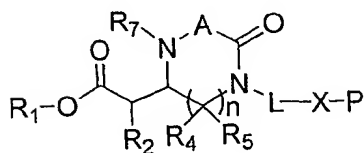
$\text{G} = \text{NR}_{18}$ ,  $\text{Q} = \text{protecting group}$   
 $\text{G} = \text{S or O}$ ,  $\text{Q} = \text{Hydrogen}$

De-protection  
 followed by  
 conjugate addition

**9-2**

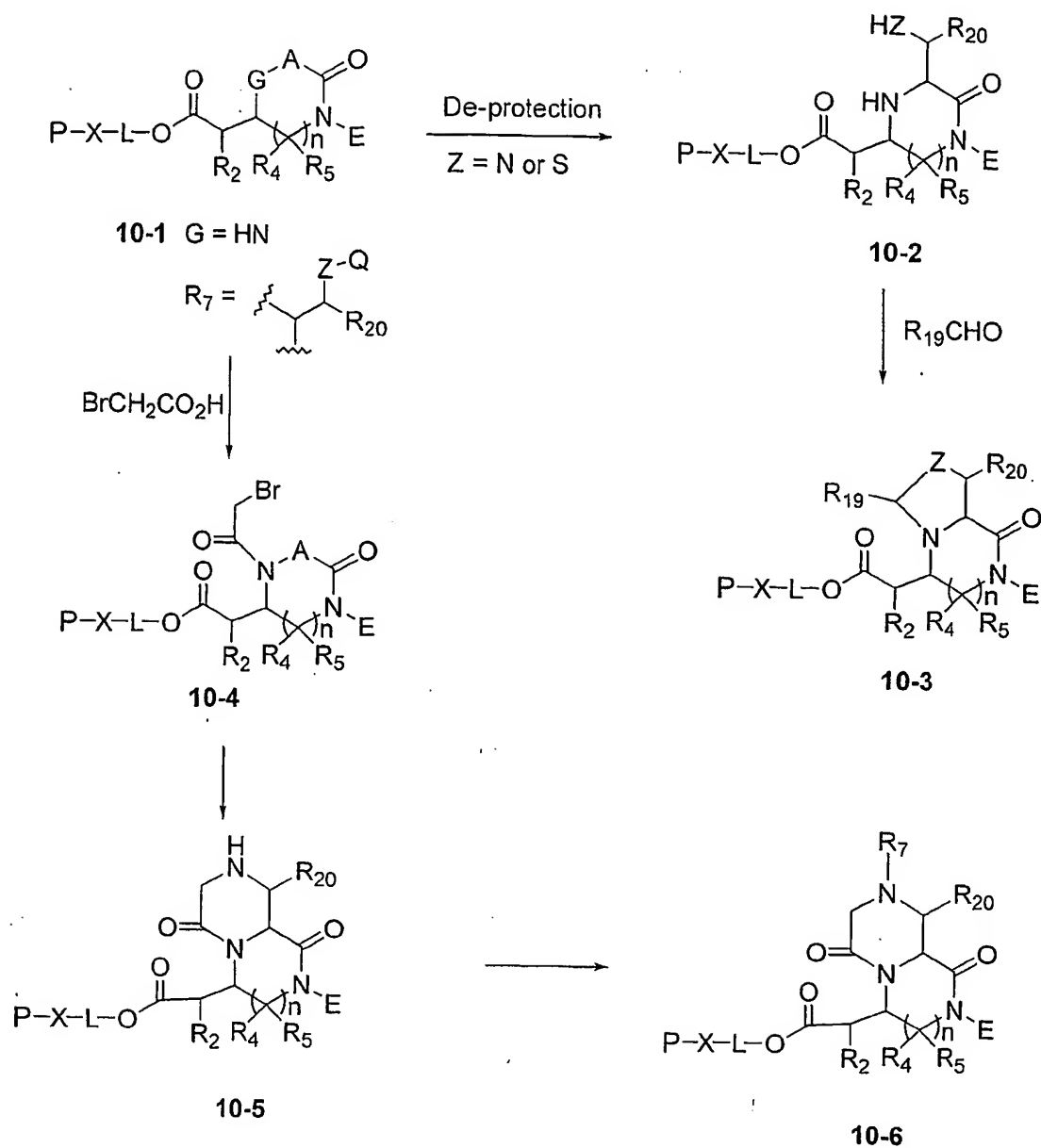
electrophilic reagents,  
 eg., isocyanates  
 acid chloride,  
 sulphonyl chloride

$\text{G} = \text{NH}$

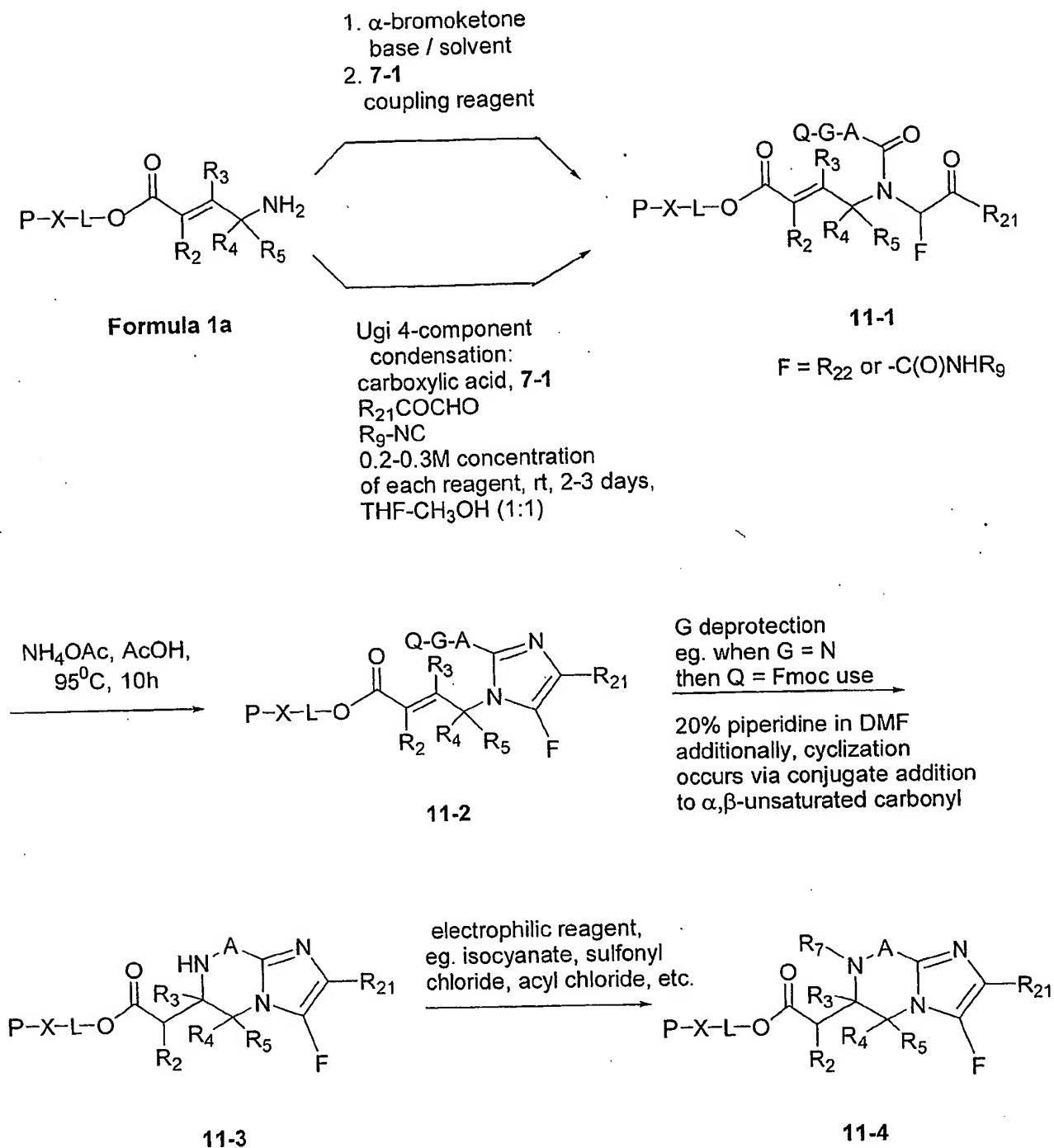
**9-3**

$\text{R}_7 = -\text{C}(\text{O})\text{NHR}_{10}$   
 $-\text{C}(\text{O})\text{R}_{11}$   
 $-\text{S}(\text{O})_2\text{R}_{12}$

**Scheme 9**

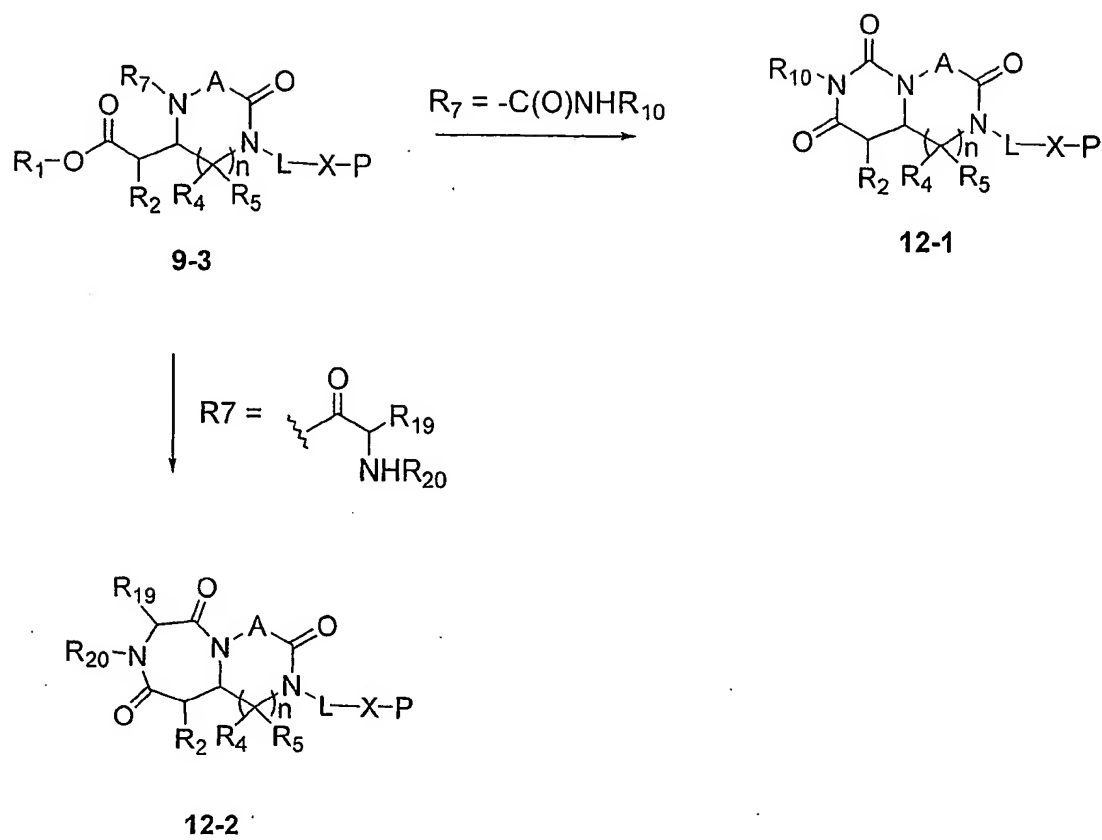


Scheme 10

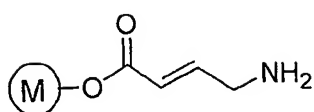
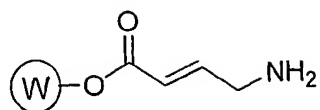
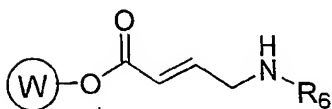
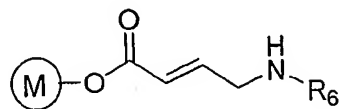
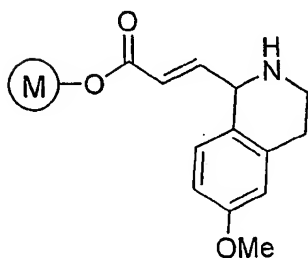
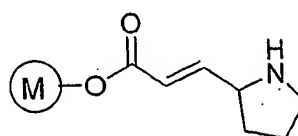
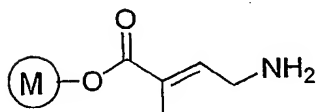
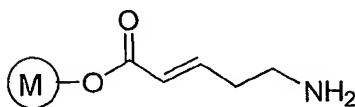
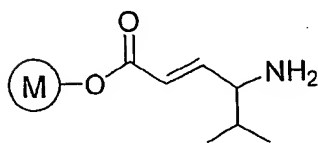
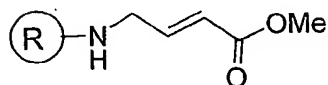


Scheme 11





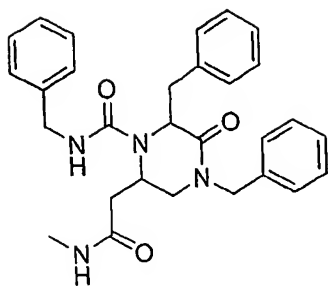
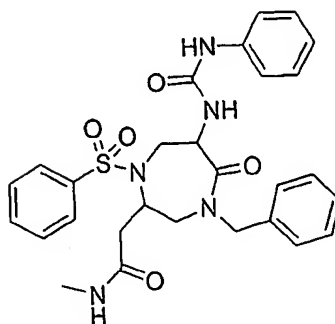
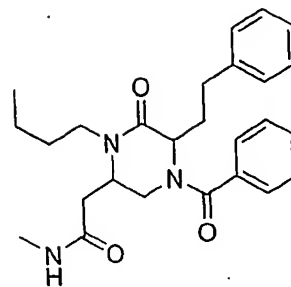
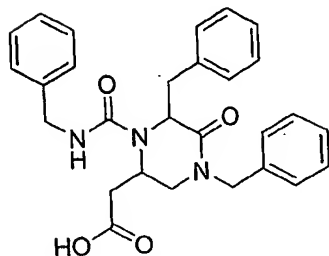
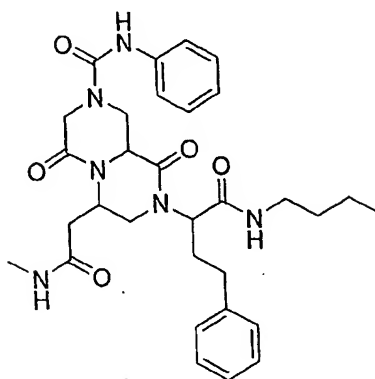
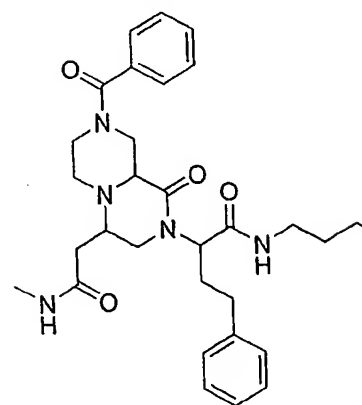
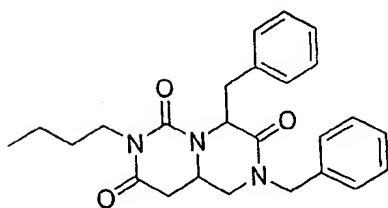
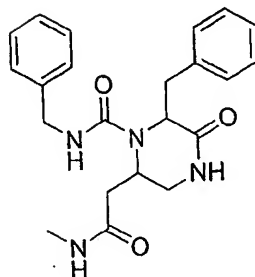
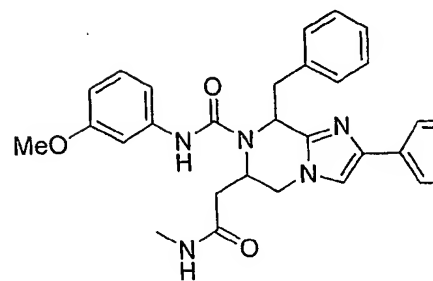
Scheme 12

Examples 1 - 10Example 1Example 2Example 3Example 4Example 5Example 6Example 7Example 8Example 9Example 10

(W) = Wang resin

(M) = Merrifield resin

(R) = Rink resin

**Examples 11 - 19****Example 11****Example 12****Example 13****Example 14****Example 15****Example 16****Example 17****Example 18****Example 19****EXAMPLES**

The following examples are by way of illustration of various aspects of the present invention and are not intended to be limiting thereof.

5 **General Procedures-Reagent Systems and Test Methods**

Anhydrous solvents were purchased from Aldrich Chemical Company and used directly. Resins were purchased from Advanced ChemTech, Louisville,

Kentucky, and used directly. The loading level ranged from 0.35 to 1.1

5 mmol/g. Unless otherwise noted, reagents were obtained from commercial suppliers and used without further purification. Preparative thin layer chromatography was performed on silica gel pre-coated glass plates (Whatman PK5F, 150 Å, 1000 µm) and visualized with UV light, and/or ninhydrin, p-anisaldehyde, ammonium molybdate, or ferric chloride. NMR spectra were  
10 obtained on a Varian Mercury 300 MHz spectrometer. Chemical shifts are reported in ppm. Unless otherwise noted, spectra were obtained in CDCl<sub>3</sub> with residual CHCl<sub>3</sub> as an internal standard at 7.26 ppm. IR spectra were obtained on a Midac M1700 and absorbencies are listed in inverse centimeters. HPLC/MS analysis were performed on a Hewlett Packard 1100 with a  
15 photodiode array detector coupled to a Micros Platform II electrospray mass spectrometer. An evaporative light scattering detector (Sedex 55) was also incorporated for more accurate evaluation of sample purity. Reverse phase columns were purchased from YMC, Inc. (ODS-A, 3 µm, 120 Å, 4.0 x 50 mm).

Solvent system A consisted of 97.5% MeOH, 2.5% H<sub>2</sub>O, and 0.05% TFA.

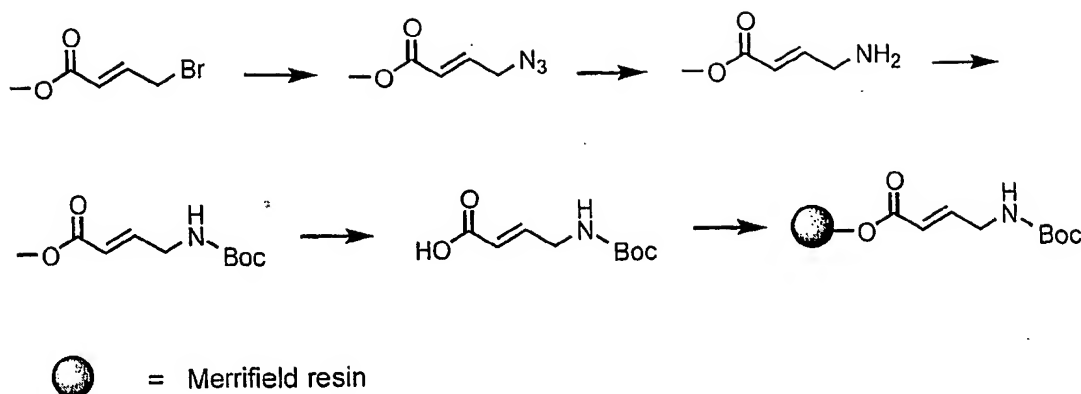
20 Solvent system B consisted of 97.5% H<sub>2</sub>O, 2.5% MeOH, and 0.05% TFA.

Samples were typically acquired at a mobile phase flow rate of 2 ml/min involving a 2 minute gradient from solvent B to solvent A with 5 minute run times. Resins were washed with appropriate solvents (100 mg of resin/ 1 ml of solvent). Technical grade solvents were used for resin washing.

25

#### Example 1

#### **Method A**



Step 1: Displacement of bromide Sodium azide (60 g, 0.92 mol) was added in small portions to a solution of methyl bromocrotonate (60mL, 0.51 mol) and ammonium chloride (6 g, 0.11 mol) in 600 mL of DMF cooled in an ice-water bath. The temperature was kept at 0~5°C during the addition of sodium azide. The stirring was continued until the reaction was completed. The reaction mixture was poured into about 600 mL of crushed ice, then extracted with 3x250 mL of EtOAc. Combined EtOAc was washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of solvent at room temperature afforded 67 g of light brown liquid whose proton NMR spectrum was consistent with expected structure.

Step 2: Reduction of the azido group The crude methyl azidocrotonate (67 g, 0.47 mol) was diluted with 500 mL of THF and 9.2 mL of water. The resulting solution was cooled over an ice-water bath, followed by addition of P(OEt)<sub>3</sub> (88mL, 0.51mol) in small portions over a 30 minutes period. The reaction mixture was then allowed to warm up to room temperature and stirred overnight. The light brown solution was concentrated and re-dissolved in 800mL of toluene and treated with hydrochloride gas for about 1 hour. The solution was capped and left at room temperature overnight. Precipitated solid was collected and washed twice with ether and dried under vacuum. 65 g of pale yellow solid was obtained. NMR indicated it was the expected product.

Step 3: Boc-protection of the amino group The aminocrotonate hydrochloride (65 g, 0.43 mol) was dissolved in a mixture of 300 mL each of 1,4-dioxane and water and cooled over an ice-water bath. To it was added 150 mL of DIEA with stirring, followed by addition of (Boc)<sub>2</sub>O (94 g, 0.43 mol) in small portions. The resulting mixture was stirred overnight. After

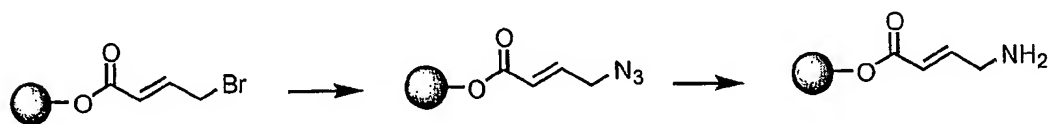
concentrated, the crude residue was extracted with 2x250 mL of EtOAc.

Combined EtOAc solution was washed with water, 10% aqueous citric acid, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of solvent afforded 80 g of light brown liquid whose proton NMR spectrum was consistent with expected structure.

5 Step 4: Hydrolysis of Boc-protected methyl aminocrotonate The crude methyl N-Boc-aminocrotonate (80 g, 0.37 mol) was dissolved in 300 mL of THF and 300 mL water. To it was added LiOH (13.5 g, 0.56 mol). The mixture was stirred overnight. Bulk of THF was removed by rotovaping. The residue was washed with ether and acidified with 10% aqueous citric acid. Then it was  
10 extracted with 3x250 mL of EtOAc. Combined EtOAc solution was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of solvent afforded 64 g of yellow solid whose proton NMR spectrum was consistent with the expected structure.

Step 5: Loading N-Boc-aminocrotonic acid onto the resin Hydroxymethyl polystyrene resin (60 g, 0.9 mmol/g, 0.054 mol), N-Boc-aminocrotonic acid (32  
15 g, 0.16 mol) and triphenylphosphine (42g, 0.16mol) were added to 600 mL of o-xylene and 250 mL of THF. The resulting slurry, under a N<sub>2</sub> atmosphere, was cooled over an ice water bath. DIAD (33 g, 0.16 mol) was added dropwise at such a rate that the reaction temperature was maintained under 10°C. After the addition of DIAD; the suspension was stirred for an additional 4 hours.  
20 The resin was collected and washed successively with DMF, DCM and MeOH several times and dried under vacuum.

### Method B



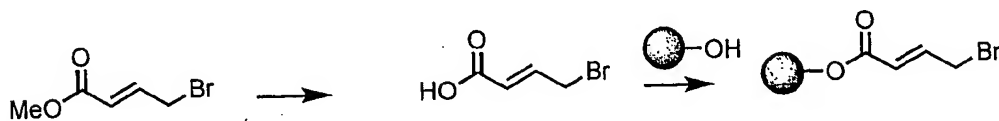
 = Merrifield resin


25 Bromocrotonate resin (10 g, 0.7 mmol/g) was added to a mixture of Bu<sub>4</sub>NHSO<sub>4</sub> (200 mg, 0.59 mmol) and NaN<sub>3</sub> (1.95 g, 30 mmol) in 130 mL of 3:1 DCM/H<sub>2</sub>O. The resulting slurry was shaken at room temperature for 45 min. The resin was filtered, washed with 1:1 MeOH/H<sub>2</sub>O (3x), DMF (3x), MeOH then

DCM (3x) and DCM (3x). the obtained resin was dried in vacuo. IR(KBr): 2105  $\text{cm}^{-1}$  ( $\text{N}_3$ ) and 1722  $\text{cm}^{-1}$  (unsaturated ester).

The above resin was then treated with 85 mL of 0.5M  $\text{SnCl}_2$  solution in 1:1 MeOH/THF pre-cooled at 0C. The suspension was warmed up to room temperature, and shaken overnight (12 h). The resin was filtered, washed with MeOH/THF (3x), 10% HOAc in 1:1 MeOH/THF (2x), DMF (3x), 0.5 M DIEA in DCM (1x), DCM then MeOH (3x) and DCM (3x). The obtained resin was dried in vacuo. IR (KBr): 1720  $\text{cm}^{-1}$ .

Preparation of 4-Bromocrotonate solid support template:



-OH = Wang resin or Hydroxymethyl resin

Methyl 4-bromocrotonate (150 g, 0.83 mol) was dissolved in 2 L of 1:1 THF and  $\text{H}_2\text{O}$ , and the solution was cooled to 0C. To this was added solid  $\text{LiOH}\cdot\text{H}_2\text{O}$  (57 g, 1.36 mol) in portions. On complete disappearance of ester as seen on TLC (4:1 hex/EtOAc) the reaction mixture was evaporated to remove THF. The remaining mixture was extracted with hexane. To the aqueous layer was added 10% HCl till pH of 3-4. The aqueous layer was extracted with EtOAc. The organic layer was then washed with water once, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give 115 g of pure product in 83% yield.

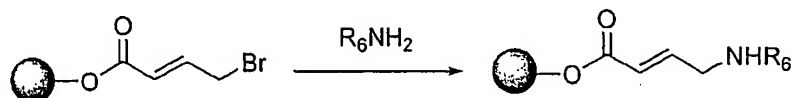
Wang resin or Hydroxymethyl polystyrene resin (200 g, 0.8 mmol/g), bromocrotonic acid (65.6 g, 0.4 mol) and triphenyl phosphine (104.9 g, 0.4 mol) were suspended in 2000 mL of anhydrous xylene under nitrogen atmosphere. The slurry was cooled in an ice bath, and diisopropyl azacarboxylate (DIAD) was added dropwise. After complete addition the reaction mixture was stirred at room temperature for 5 h. The resin was then filtered, washed with DMF

(3x), DCM then MeOH (3x) and DCM (3x). The obtained resin was dried in vacuo. IR (KBr): 1718  $\text{cm}^{-1}$  (unsaturated ester).

### Example 2

Wang resin was used as the polymer support. The same method was followed as described for the preparation of the Example 1.

### Example 3

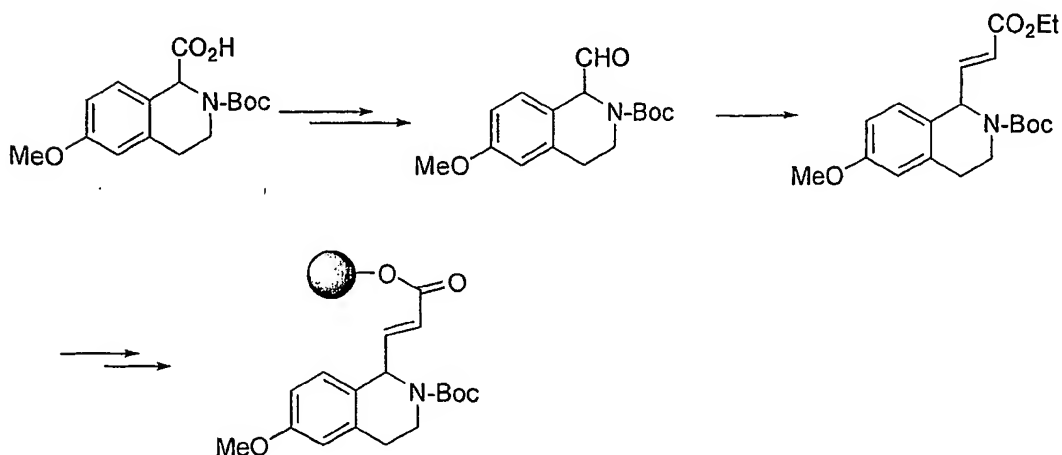


4-Bromocrotonate Wang Resin (3 g, loading 0.9 mmol/g) was suspended in a solution of an appropriate amine [0.5 M] in NMP (40 mL) and shaken for 45 min at room temperature. After filtration, the resulting mixture was washed by 2x10 mL of DMF, 3x10 mL of DCM/MeOH, 2x10 mL of DCM then dried under nitrogen. IR(KBr): 1718  $\text{cm}^{-1}$ .

### Example 4

The same method was followed as described for the preparation of the Example 3. In this case, 4-bromocrotonate Merrifield resin was used.

### Example 5





The Boc amino acid (6.2 g, 20.2 mmol) was dissolved in 10 mL of THF, the resulting solution was cooled to 0°C. To this solution was added dropwise 40 mL of a 1M solution of  $\text{BH}_3 \cdot \text{THF}$  in THF with the formation of bubbles. After completion of the addition, stirring continued at the same temperature for 30 min, then it was warmed to room temperature and stirred for another 3 h. The mixture was concentrated to give a residue which was dissolved in EtOAc. The organic solution was washed with water, sat.  $\text{NaHCO}_3$  and brine. The dried organic layer was concentrated to give the crude product (5.2 g).

The above obtained alcohol (1 g) was dissolved in 10 mL of DCM. A mixture of 1:1 10% NaBr and sat.  $\text{NaHCO}_3$  was added. After the mixture was cooled to 0°C, bleach (commercially available, 5.1 mL) and a catalytic amount of TEMPO were added. The mixture was then stirred for 30 min. It was diluted with EtOAc. The organic was washed with diluted  $\text{Na}_2\text{S}_2\text{O}_3$  solution, water and brine. Concentration gave the crude aldehyde.

To a solution of the above obtained crude aldehyde in 35 mL of  $\text{CH}_3\text{CN}$  was added (carbethoxymethylene)-triphenylphosphorane (1.54 g). The resulting mixture was stirred at room temperature for 16 h. Concentration gave a residue which was purified by flash chromatography on silica gel using EtOAc/hex (1:8 to 1:3) to afford the desired  $\alpha,\beta$ -unsaturated ester as a colorless oil (570 mg), confirmed by LC-MS and  $^1\text{H}$ NMR analysis.

The  $\alpha,\beta$ -unsaturated ester (500 mg) was dissolved in 10 mL of a mixture of dioxane/ $\text{H}_2\text{O}$  (2:1). Lithium hydroxide monohydrate (85 mg) was added. The mixture was stirred at rt for 2 h at which time TLC indicated the starting material had been consumed. The mixture was concentrated under reduced pressure to remove dioxane. The residue was treated with 10% citric acid, extracted with EtOAc. The organic layer was washed with water and then brine. Drying ( $\text{Na}_2\text{SO}_4$ ) followed by concentration gave the pure carboxylic acid (450 mg), confirmed by LC-MS and  $^1\text{H}$ NMR analysis.

The coupling of the carboxylic acid to hydroxymethyl resin was achieved under the standard condition. A suspension of 450 mg of the acid obtained above and hydroxymethyl resin (560 mg, 0.8 mmol/g) in THF (6 mL) were added DIC (0.21 mL) and DMAP (50 mg). The resulting suspension was shaken at rt for 12 h. The resin was filtered, washed with DMF (2x), DCM (3x),

MeOH/DCM (alternatively, 3x), DCM (3x). The resin was dried under reduced pressure (780 mg).

The removal of Boc protecting group was carried out by the treatment of the resin with 20% TFA in DCM at rt for 30 min. A regular washing procedure was followed. The final de-protected resin was obtained after dryness. IR(KBr): 1720  $\text{cm}^{-1}$ .

#### Example 6

The same method as described above for the preparation of Example 5 was followed. The desired templates were obtained from the corresponding Boc-prolinal.

#### Example 7

The same method as described above for the preparation of Example 4 was followed. The desired templates were obtained from the corresponding N-Boc-2-aminoacetaldehyde.

#### Example 8

The same method as described above for the preparation of Example 4 was followed. The desired templates were obtained from the corresponding N-Boc-3-aminopropionaldehyde.

#### Example 9

The same method as described above for the preparation of Example 4 was followed. The desired templates were obtained from the corresponding Boc-valinal.

#### Example 10

Rink resin (3.5 g, 0.7 mmol/g) was added to a mixture of THF (10 mL), a 1 M solution of methyl 4-bromocrotonate in THF (14.7 mL) and 1 M DIEA in THF (3.7 mL). The suspension was shaken at rt for 6 h. The resin was then filtered, and washed with DMF (3x), MeOH/DCM (3x), DCM (3x), dried under reduced pressure. IR(KBr): 1718  $\text{cm}^{-1}$ .

#### Example 11

Solid phase synthesis of a piperazinone derivative, Example 11, based on the method described in Scheme 7:

Step 1: Displacement of bromide 4-Bromocrotonate Merrifield or Wang Resin (300 mg, loading 0.9 mmol/g) was suspended in a solution of benzylamine [0.5M] in NMP (8 mL) and shaken for 45 min at room temperature. After filtration, the resulting mixture was washed by 2x10 mL of DMF, 3x10 mL of DCM/MeOH, 2x10 mL of DCM then dried under nitrogen flow. IR(KBr): 1718  $\text{cm}^{-1}$ .

Step 2: Acylation To the resin were added Fmoc-L-phenylalanine (10 eq), DIC (10 eq), and DMF (3 mL / 100 mg of resin). The resulting mixture was shaken for 24 h at room temperature. After filtration, the resin was washed with 2xDMF (3 mL / 100 mg of resin), 2xDCM/MeOH, 2xDCM then dried under nitrogen flow.

Step 3: Deprotection and cyclization The resin was suspended in a solution of piperidine (20%) in DMF (3 mL / 100 mg of resin) and shaken for 30 min. After filtration, the resin was washed with 2xDMF (3 mL / 100mg of resin), 2xDCM/MeOH, 2xDCM then dried under nitrogen flow. IR (KBr): 1734  $\text{cm}^{-1}$ .

Step 4: Formation of urea The resin was suspended in a solution of benzyl isocyanate [0.5M] in DCE (3 mL / 100 mg of resin) and shaken for 12 h at room temperature. The resin was filtered and washed by 2xDME, 2xDCM/MeOH, 2xDCM then dried under nitrogen flow.

Step 4: Alternative method for the formation of urea The resin was suspended in a solution of 0.1 M DIEA in DCE (1 mL/100 mg resin). A solution of 0.1 M triphosgene (0.5 mL/100mg resin) was then added. After shaking at rt for 4 h, a solution of 1 M benzylamine in DMF (0.3 mL) was added. Shaking continued overnight. The resin was filtered and washed with 2xDMF, 3xDCM/MeOH, 3xDCM then dried under nitrogen.

Step 5: Cleavage of the product The resin was suspended in a 1:1 mixture of methylamine (40% in  $\text{H}_2\text{O}$ )/THF (3 mL per 100 mg of resin) and shaken for

24h. After filtration, the resin was washed by 2xDCM (3 mL / 100 mg of resin). The volatiles were removed under reduced pressure to afford crude product. After purification on a preparative TLC plate, the pure desired compound were isolated as a mixture of two isomers with a 2:1 ratio (>85% yield, based on

5 0.9mmol/g loading).

MS (ES)  $m/e$  (relative intensity): 4485 ( $M+H^+$ , 100).

### Example 12

Solid phase synthesis of a diazepine derivative, Example 12, based on the  
10 method described in Scheme 7:

Step 1: Displacement of bromide 4-Bromocrotonate Merrifield Resin (300 mg, loading 0.9 mmol/g) was suspended in a solution of benzylamine [0.5M] in

15 NMP (8 mL) and shaken for 45 min at room temperature. After filtration, the resulting mixture was washed by 2x10 mL of DMF, 3x10 mL of DCM/MeOH, 2x10 mL of DCM then dried under nitrogen. IR(KBr): 1718  $\text{cm}^{-1}$ .

Step 2: Acylation To the resin were added  $N^{\alpha}$ -Boc- $N^{\beta}$ -Fmoc-diamino-propionic acid (6 eq), DIC (6 eq), and DMF (3 mL / 100 mg of resin). The resulting mixture was shaken for 24 h at room temperature. After filtration, the resin  
20 was washed with 2xDMF (3 mL / 100 mg of resin), 2xDCM/MeOH, 2xDCM then dried under nitrogen.

Step 3: Deprotection and cyclization The resin was suspended in a solution of piperidine (20%) in DMF (3 mL / 100 mg of resin) and shaken for 30 min. After filtration, the resin was washed with 2xDMF (3 mL / 100mg of  
25 resin), 2xDCM/MeOH, 2xDCM then dried under nitrogen flow. IR (KBr): 1734  $\text{cm}^{-1}$ .

Step 4: Sulphonylation The resin was suspended in a mixture of 3:2 pyridine/DCM (0.5 mL / 100 mg of resin), a solution of 0.5 M phenylsulfonyl chloride in DCE (0.5 mL) was added. The resulting slurry was shaken at room  
30 temperature for 12 h. The resin was then filtered, washed with DMF (3x), DCM/MeOH (alternatively, 3x) and DCM (3x). The same process was repeated in order to drive the sulfonylation to be complete.

Step 5: De-Boc protection and formation of urea The resin was treated with 20% TFA in DCM for 30 min, then filtered and washed successively with

DCM, neutralized with 1M DIEA in DCM. The resin was suspended in a solution of phenyl isocyanate [0.5M] in DCE (3 mL / 100 mg of resin) and shaken for 12 h at room temperature. The resin was filtered and washed by 2xDME, 2xDCM/MeOH, 2xDCM then dried under nitrogen.

- 5 Step 6: Cleavage of the product The resin was suspended in a 1:1 mixture of methylamine (40% in H<sub>2</sub>O)/THF (3 mL per 100 mg of resin) and shaken for 24h. After filtration, the resin was washed by 2xDCM (3 mL / 100 mg of resin). The volatile was removed under reduced pressure to afford crude product. After purification on a preparative TLC plate, the pure desired compound were
- 10 isolated as a mixture of two isomers with a 2:1 ratio (62%, based on 0.9mmol/g loading). MS (ES) *m/e* (relative intensity): 550 (M+H<sup>+</sup>, 90).

### Example 13

Solid phase synthesis of a piperazinone derivative, Example 13, based on the

15 method described in Scheme 8:

Step 1 4-Aminocrotonate Merrifield resin (100 mg, 0.8 mmol/g) was suspended in a mixture of benzoic acid (0.8 M in THF, 1.0 mL), n-butyl isocyanide (2.0 M in MeOH, 0.4 mL), dihydrocinnamaldehyde (2.0M in MeOH, 0.4 mL). The mixture was shaken at rt for 2 days. The resin was filtered and

20 washed with MeOH (3x), DMF (2x), MeOH/DCM (alternatively, 3x), DCM (3x).

Step 2-3 The resin was treated with 2.0 mL of 1M DBU in THF for 24 h, then filtered and washed by using the standard protocol. The obtained resin was treated with a 1:1 mixture of methylamine (40% in H<sub>2</sub>O)/THF (3 mL ) and the mixture was shaken for 24 h. After filtration, the resin was rinsed with

25 2xDCM (3 mL / 100 mg of resin). The volatile was removed under reduced pressure to afford crude product. After purification on a preparative TLC plate, the pure desired compound was isolated as a mixture of two isomers (56 %, based on 0.8 mmol/g loading). MS (ES) *m/e* (relative intensity): 436 (M+H<sup>+</sup>).

### Example 14

Solid phase synthesis of a piperazinone derivative, Example 14, based on the

30 method described in Scheme 7:

Step 1 – 4: Starting from 4-bromocrotonate Wang Resin, the same procedure was followed as described for the preparation of Example 11.

Step 5: Cleavage of the product The resin was suspended in a mixture of TFA (25%) in DCM (3 mL / 100mg of resin) and shaken for 30 min. After filtration, the resin was washed by 2xDCM (3 mL / 100mg of resin). The volatiles were removed under reduced pressure to lead to crude xx mg. Purification via the ester (treatment of the crude by TMSCHN<sub>2</sub>) afforded 25 mg of pure desired compound as a mixture of two isomers with a 2:1 ratio (39%, based on 0.9 mmol/g loading). MS (ES) *m/e* (relative intensity): 472 (M+H<sup>+</sup>, 100).

0

### Example 15

Solid phase synthesis of a piperazino-piperazine derivative, Example 15, based on the method described in Scheme 10:

- 15 Step 1: Ugi reaction Ugi reaction was carried out under the same conditions described in the first step of the Example 13. The four components used in the reaction included: 4-aminocrotonate Merrifield resin (200 mg, 0.8 mmol/g), N<sup>α</sup>-Fmoc-N<sup>β</sup>-Boc-diaminopropionic acid, dihydrocinnam-aldehyde and n-butyl isocyanide
- 20 Step 2: De-Fmoc protection The resin was suspended in a solution of piperidine (20%) in DMF (3 mL / 100 mg of resin) and shaken for 30 min. After filtration, the resin was washed with 2xDMF (3 mL / 100mg of resin), 2xDCM/MeOH, 2xDCM then dried under nitrogen.
- 25 Step 3: Acylation with α-bromoacetic acid To the resin were added bromoacetic acid (10 eq), DIC (10 eq), and DMF (3 mL / 100 mg of resin). The resulting mixture was shaken for 3 h at room temperature. After filtration, the resin was washed with 2xDMF (3 mL / 100 mg of resin), then the same process was repeated in order to achieve the reaction completion.
- 30 Step 4: De-Boc protection and cyclization The resin was treated with 20% TFA in DCM for 30 min, then filtered and washed successively with DCM, neutralized with 1M DIEA in DCM. The resin was suspended in 1 M DIEA in DCM. After shaking for 3 h, it was filtered and washed by using the standard protocols.

Step 5: Formation of urea The resin was treated with a solution of phenyl isocyanate [0.5M] in DCE (3 mL / 100 mg of resin) and shaken for 12 h at room temperature. The resin was filtered and washed by 2xDME, 2xDCM/MeOH, 2xDCM then dried under nitrogen.

- 5 Step 6: Cleavage of the product The resin was suspended in a 1:1 mixture of methylamine (40% in H<sub>2</sub>O)/THF (3 mL per 100 mg of resin) and shaken for 24h. After filtration, the resin was washed by 2xDCM (3 mL / 100 mg of resin). The volatile was removed under reduced pressure to afford crude product. After purification on a preparative TLC plate, the pure desired compound were  
10 isolated as a mixture of two isomers with a 2:1 ratio (45%, based on 0.8 mmol/g loading).

### Example 16

- 15 Solid phase synthesis of a piperazino-piperazine derivative, Example 16, based on the method described in Scheme 7:

- Step 1: Ugi reaction Ugi reaction was carried out under the same conditions described in the first step of the Example 13. The four components used in the reaction included: 4-aminocrotonate Merrifield resin (200 mg, 0.8  
20 mmol/g), N<sup>□</sup>-Fmoc-N<sup>□</sup>-Boc-piperazine-2-carboxylic acid (5 equiv.), dihydrocinnam-aldehyde (10 equiv.) and n-butyl isocyanide (10 equiv.).

- Step 2: De-Fmoc protection and cyclization The resin was suspended in a solution of piperidine (20%) in DMF (3 mL / 100 mg of resin) and shaken for 30 min. After filtration, the resin was washed with 2xDMF (3 mL / 100mg of  
25 resin), 2xDCM/MeOH, 2xDCM then dried under nitrogen flow.

- Step 3: De-Boc protection and acylation The resin was treated with 20% TFA in DCM for 30 min, then filtered and washed successively with DCM, neutralized with 1M DIEA in DCM. To the resin were added benzoic acid (10 eq), DIC (10 eq), and DMF (3 mL / 100 mg of resin). The resulting mixture was  
30 shaken overnight at room temperature. After filtration, the resin was washed with 2xDMF (3 mL / 100 mg of resin).

Step 4: Cleavage of the product The resin was suspended in a 1:1 mixture of methylamine (40% in H<sub>2</sub>O)/THF (3 mL per 100 mg of resin) and shaken for 24h. After filtration, the resin was washed by 2xDCM (3 mL / 100 mg of resin).

The volatile was removed under reduced pressure to afford crude product. After purification on a preparative TLC plate, the pure desired compound were isolated as a mixture of two isomers with a 2:1 ratio (70%, based on 0.8 mmol/g loading).

5

### Example 17

Solid phase synthesis of a piperazino-hydantoin derivative, Example 17, based on the method described in Scheme 12:

10

Step1 - 4 The same procedure was followed as described in the Example 11 (step1-4).

Step 5: Cleavage of the product The resin was suspended in neat TFA (6 mL / 100 mg), and shaken for 12 h, then filtered. The resin was rinsed with DCM, and the combined filtrates were concentrated to give a crude product which was analyzed by LC-MS and <sup>1</sup>HNMR (>95% purity, >60% yield).

15

### Example 18

Solid phase synthesis of a piperazinone derivative, Example 18, based on the method described in Scheme 9:

20

Step 1: Acylation and cyclization The solid support template, Example 10 (200 mg) was mixed with 1M DIC in DMF (1.6 mL) and 1 M Fmoc-Phe-OH in DMF (1.6 mL). After shaking for 24 h at rt, filtration followed by washing (DMF, MeOH/DCM and DCM, 3x) gave the resin which was then treated with 20% piperidine in DMF. After stirring for 30 min at rt, the resin was filtered and washed as usual. The resin was dried under reduced pressure.

25

Step 2: Formation of urea The resin was treated with a solution of benzyl isocyanate [0.5M] in DCE (3 mL / 100 mg of resin) and shaken for 12 h at room temperature. The resin was filtered and washed by 2xDME, 2xDCM/MeOH, 2xDCM then dried under nitrogen.

30

Step 3: Formation of amide The resin was suspended in a 1:1 mixture of methylamine (40% in H<sub>2</sub>O)/THF (3 mL per 100 mg of resin) and shaken for 24h. After filtration, the resin was washed by DMF (3x), MeOH (3x) and DCM (3x), and dried under a nitrogen flow.



Step 4: Cleavage of the product The resin was treated with 20% TFA in DCM for 20 min. Filtration followed by washing with DCM gave a filtrate which was concentrated to give the crude product, confirmed by LC-MS and <sup>1</sup>HNMR analysis.

### Example 19

Solid phase synthesis of a imidazo-piperazine derivative, Example 19, based on the method described in Scheme 11:

Step 1: Alkylation with  $\alpha$ -bromoketone 4-Aminocrotonate Merrifield resin

(188 mg, 0.11 mmol) was mixed with 2-bromoacetophenone (0.5 M in THF, 0.55 mL) and DIEA (1 M in THF, 0.275 mL). The suspension was shaken at rt for 2.5 h. The resin was then filtered, washed with THF (3x), MeOH (3x) and DCM (3x). The resin was dried *in vacuo*. IR (KBr): 1700 cm<sup>-1</sup> (ketone).

Step 2: Acylation To the above obtained resin were added 1M Boc-Phe-OH in DMF (1.0 mL), 1M DIC in DMF (1.0 mL) and 1M HOBt in DMF (0.1 mL). The resulting suspension was shaken at rt for 12 h. Filtration followed by standard washing gave the resin which was dried under a nitrogen flow.

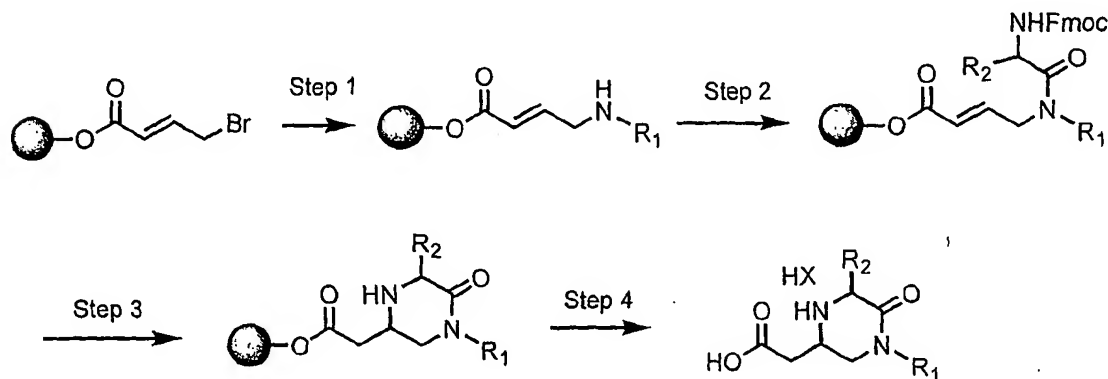
Step 3: Formation of imidazole To the resin was added 2 mL of sat. NH<sub>4</sub>OAc in HOAc (50 g in 120 mL of HOAc). The mixture was heated with vigorously stirring for 8 h. After cooling to rt, the resin was filtered and washed with HOAc (2x), DMF (2x), MeOH (3x), DCM (3x).


Step 4: Deprotection and cyclization The above resin was then treated with 20% TFA in DCM for 30 min, then filtered and washed as usual. To the resin was added 20% piperidine in DMF, the mixture was shaken for 30 min followed by the standard washing and drying procedure.

Step 5: Cleavage of the product The resin obtained above (100 mg) was treated with a solution of 0.5 M 3-methoxyphenyl isocyanate in DCE (2.0 mL) at rt overnight. The standard washing and drying protocol were followed. The resin was then treated with a 1:1 mixture of methylamine (40% in H<sub>2</sub>O)/THF (3 mL per 100 mg of resin) and shaken for 24h. After filtration, the resin was washed by 2xDCM (3 mL / 100 mg of resin). The volatile was removed under reduced pressure to afford crude product. After purification on a preparative TLC plate, the pure desired compound was obtained in 35% yield. MS (ES) *m/e* (relative intensity): 510 (M+H<sup>+</sup>, 100).

Example 20

Solid phase synthesis of an array of 5-oxo-piperazin-2-yl-acetic acids based on the method described in Scheme 7:



 = Wang resin

A 96-compound library was synthesized in a 96-well reaction block on an ACT synthesizer. Reagents were dispensed according to the following arrangement:

Block: 4-Bromocrotonate Wang resin (5 g, 0.8 mmol/g);

10 Rows: Fmoc-amino acids (0.8 M in THF, 0.5 mL/well);

Columns: amines (1 M in NMP, 0.5 mL/well).

<u>Columns</u>	<u>Rows</u>
#1 n-butylamine	#1 Fmoc-Ala-OH
#2 iso-propylamine	#2 Fmoc-Val-OH
#3 benzylamine	#3 Fmoc-Leu-OH
#4 cyclohexylamine	#4 Fmoc-Ile-OH
#5 4-methoxybenzylamine	#5 Fmoc-Phe-OH
#6 phenethylamine	#6 Fmoc-Trp-OH
#7 tetrahydrofurfurylamine	#7 Fmoc-Gly-OH
#8 allylamine	#8 Fmoc-Asp(tBu)-OH

	#9 Fmoc-Phg-OH
	#10 Fmoc-Ser(Bn)-OH
	#11 Fmoc-Tyr(tBu)-OH
	#12 Fmoc-Nle-OH

Step 1: 4-Bromocrotonate Wang resin (Example X) (5 g, 0.8 mmol/g) was suspended in a mixture of DCM and THF (ca. 3:2, v/v, 100 mL), and evenly dispensed into 96 reaction wells in the reaction block (1mL/well). The resin was then dried by applying nitrogen flow and emptying the reaction block on an ACT synthesizer. An array of eight amine solutions was dispensed into the eight vertical columns (one amine/column) of the block in an order described above. The reaction block was shaken at rt for 45 min, then emptied. The remaining resin was washed as usual with DMF (2x), DCM (3x), MeOH (3x) and DCM (3x).

Step 2: An array of 12 Fmoc-amino acids was dispensed into 12 horizontal rows (one Fmoc-amino acid/row) of the block in an order described above, followed by an addition of DIC solution (2 M in DMF, 0.2 mL/well). The reaction block was then shaken at rt overnight. After emptying the block, the remaining resin was washed as usual with DMF (2x), DCM (3x), MeOH (3x) and DCM (3x).

Step 3: A solution of 20% piperidine in DMF (1.5 mL/well) was dispensed into the 96-well reaction block. The reaction block was shaken at rt for 30 min. After emptying the block, the remaining resin was washed with DMF (2x), DCM (3x), MeOH (3x) and DCM (3x).

Step 4: The 96 products were cleaved from the resin by the treatment with 20% TFA in DCM at room temperature for 30 min. The cleavage solutions were collected into 96 cleavage vials. The remaining resin was rinsed with DCM (1mL/well). The combined solutions were concentrated under the reduced pressure in a GeneVac to give a library of 96 compounds.

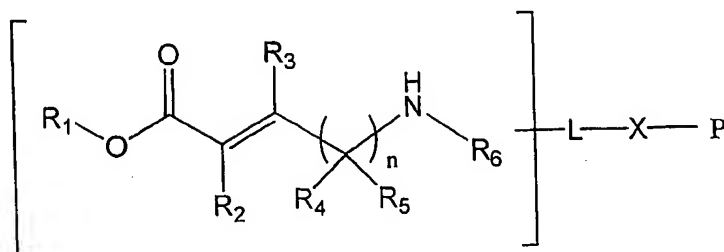
Analytical Results (20 compounds were randomly chosen for LC-MS analysis):

Entry	Amines	Fmoc-amino acids	Purity <sup>a</sup>	Yield <sup>b</sup>
1	n-butylamine	Fmoc-Ala-OH	60%	86%
2	Phenethylamine	Fmoc-Ala-OH	70%	90%
3	Benzylamine	Fmoc-Val-OH	80%	79%
4	Allylamine	Fmoc-Val-OH	60%	70%
5	4-methoxybenzylamine	Fmoc-Leu-OH	80%	87%
6	Isopropylamine	Fmoc-Ile-OH	80%	81%
7	Tetrahydrofurfurylamine	Fmoc-Ile-OH	90%	81%
8	Cyclohexylamine	Fmoc-Phe-OH	>95%	84%
9	n-butylamine	Fmoc-Trp-OH	50%	16%
10	Phenethylamine	Fmoc-Trp-OH	80%	20%
11	Benzylamine	Fmoc-Gly-OH	90%	84%
12	Allylamine	Fmoc-Gly-OH	70%	61%
13	4-methoxybenzylamine	Fmoc-Gly-OH	90%	57%
14	Isopropylamine	Fmoc-Phg-OH	80%	86%
15	Tetrahydrofurfurylamine	Fmoc-Phg-OH	80%	90%
16	Cyclohexylamine	Fmoc-Ser(OBn)-OH	90%	59%
17	n-butylamine	Fmoc-Tyr(tBu)-OH	90%	53%
18	Phenethylamine	Fmoc-Tyr(tBu)-OH	90%	74%
19	Benzylamine	Fmoc-Nle-OH	80%	68%
20	Allylamine	Fmoc-Nle-OH	80%	52%

- <sup>a</sup> Purity was determined by LC-MS analysis under conditions described in the general procedures; <sup>b</sup> yield of the crude product.

Having described the invention we claim:

1. A substituted  $\alpha,\beta$ -unsaturated ester template of the general formula



where:

P is an insoluble substrate;

n is 1 or 2;

X is selected from the group consisting of a covalent bond, an atom or a functional group connecting insoluble substrate and said linker;

R<sub>1</sub> is selected from a group consisting of covalent bond, hydrogen, substituted alkylsilyl, substituted alkyl, substituted alkenyl;

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from a group consisting of a covalent bond, hydrogen, substituted alkyl, substituted alkenyl, substituted alkenylaryl, substituted alkynyl, substituted aryl, substituted alkylaryl, substituted cycloalkyl and substituted alkylcycloalkyl, substituted amino, substituted hydroxyl, substituted sulfhydryl, substituted alkylsulfonamido, substituted alkylcarbonylamino, substituted alkylaminocarbonylamino, substituted alkylsulfamido, substituted alkyloxycarbonylamino, substituted arylalkylsulfonamido, substituted arylalkylcarbonylamino, substituted arylalkylaminocarbonylamino, substituted arylalkylsulfamido and substituted arylalkyloxycarbonyl-amino;

R<sub>1</sub> taken in combination with either of R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are substituted cycloalkyl and substituted saturated heterocycles;

R<sub>2</sub> taken in combination with either of R<sub>3</sub>, R<sub>4</sub> and R<sub>6</sub> are substituted cycloalkyl and substituted saturated heterocycles;

R<sub>3</sub> taken in combination with either of R<sub>4</sub> and R<sub>6</sub> are substituted cycloalkyl and substituted saturated heterocycles;

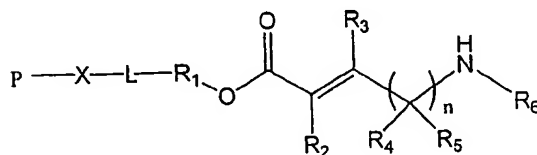
R<sub>5</sub> and R<sub>6</sub> taken in combination, are substituted cycloalkyl and substituted saturated heterocycles;

L is a linker selected from the group consisting of a covalent bond, an atom, a multifunctional chemical monomer or combinations thereof in which one functional group is coupled with X and the other functional groups react with one of said R groups; and

one of said R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> is attached to said insoluble substrate through said linker L.

2. The template of claim 1 wherein said insoluble substrate is selected is selected from the group consisting of cellulose, pre-glass beads, silica gels, polypropylene, polyacrylamide and polystyrene.
3. The template of claim 1 wherein said substrate is polystyrene lightly cross-linked with 1-2% divinylbenzene and functionalized with groups selected from amino, hydroxy, carboxy or halo groups and combinations thereof.
4. The template of claim 3 wherein said substrate is grafted with polyethylene glycol.

5. A solid support template comprising a template composition attached to a polymer backbone P for the synthesis of chemical compounds, said support having the formula:

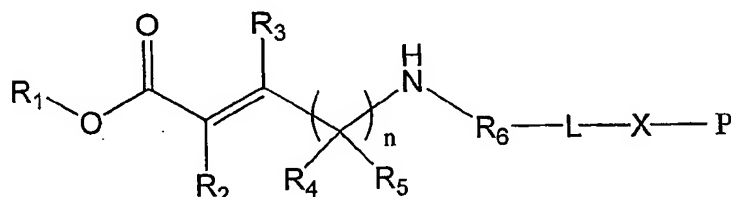


wherein;

X is a moiety that forms a covalent bond to join said polymer backbone and said template composition, L is selected from the group consisting of a covalent bond, an atom, a multifunctional monomer carrying a first functional group that forms a covalent bond with X and a second functional group for reaction with said template composition to attach said template composition to said polymer backbone and combinations thereof; R<sub>1</sub> is selected from a group consisting of a covalent bond, alkyl, alkyl-aryl, alkenyl, alkenyl-aryl and alkylsilyl groups and substituted forms thereof; R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from a group consisting of hydrogen, substituted alkyl, substituted alkenyl, substituted alkenylaryl, substituted alkynyl, substituted aryl, substituted alkylaryl, substituted cycloalkyl, substituted alkylcycloalkyl substituted amino, substituted hydroxyl, substituted sulfhydryl, substituted alkylsulfonamido, substituted alkylcarbonylamino, substituted alkylaminocarbonylamino, substituted alkylsulfamido, substituted alkyloxycarbox-amido, substituted arylalkylsulfonamido, substituted arylalkylcarbonylamino, substituted arylalkylaminocarbonylamino, substituted arylalkylsulfamido and substituted arylalkyloxycarbonylamino; R<sub>1</sub> taken in combination with either of R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are

substituted cycloalkyl and substituted saturated heterocycles;  
 $R_2$  taken in combination with either of  $R_3$ ,  $R_4$  and  $R_6$  are  
 substituted cycloalkyl and substituted saturated heterocycles;  
 $R_3$  taken in combination with either of  $R_4$  and  $R_6$  are  
 substituted cycloalkyl and substituted saturated heterocycles;  
 $R_5$  and  $R_6$  taken in combination, are substituted cycloalkyl  
 and substituted saturated heterocycles and  $n$  is 1 or 2.

6. The solid support of claim 5 wherein  $X$  is a functional group selected from the group consisting of oxygen, ester, amide, sulfur, silicon and carbon.
7. The solid support of claim 1 wherein  $L$  is linked to  $R_6$  as represented by the formula:



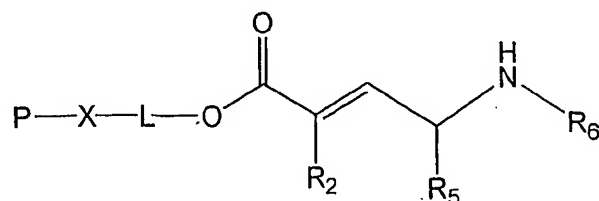
wherein;

$X$  is a moiety that forms a covalent bond to join said polymer backbone  $P$  and said template composition,  $L$  is selected from the group consisting of a covalent bond, an atom, a multifunctional monomer carrying a first functional group that forms a covalent bond with  $X$  and a second functional group for reaction with said template composition to attach said template composition to said polymer backbone and combinations thereof;  $R_6$  is selected from a group consisting of covalent bond, alkyl, alkyl-aryl, alkenyl, alkenyl-aryl and



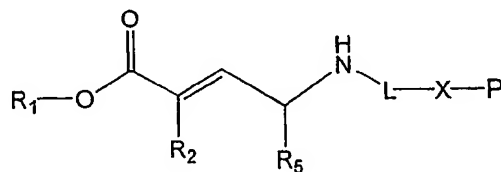
alkylsilyl groups and substituted forms thereof; R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are independently selected from a group consisting of hydrogen, substituted alkyl, substituted alkenyl, substituted alkenylaryl, substituted alkynyl, substituted aryl, substituted alkylaryl, substituted cycloalkyl, substituted alkylcycloalkyl substituted amino, substituted hydroxyl, substituted sulfhydryl, substituted alkylsulfonamido, substituted alkylcarbonylamino, substituted alkylaminocarbonylamino, substituted alkylsulfamido, substituted alkyloxycarbox-amido, substituted arylalkylsulfonamido, substituted arylalkylcarbonylamino, substituted arylalkylaminocarbonylamino, substituted arylalkylsulfamido and substituted arylalkyloxycarbonylamino; R<sub>1</sub> taken in combination with either of R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are substituted cycloalkyl and substituted saturated heterocycles; R<sub>2</sub> taken in combination with either of R<sub>3</sub>, R<sub>4</sub> and R<sub>6</sub> are substituted cycloalkyl and substituted saturated heterocycles; R<sub>3</sub> taken in combination with either of R<sub>4</sub> and R<sub>6</sub> are substituted cycloalkyl and substituted saturated heterocycles; R<sub>5</sub> and R<sub>6</sub> taken in combination, are substituted cycloalkyl and substituted saturated heterocycles and n is 1 or 2.

8. The solid support of claim 5 as represented by the formula:



wherein:  $R_1$  is a covalent bond; and  $R_3$  and  $R_4$  are hydrogen,  
 $R_2$ ,  $R_5$ , and  $R_6$  are independently selected from a group  
 consisting of hydrogen, substituted amino, substituted  
 hydroxyl, substituted alkyl, substituted alkenyl, substituted  
 alkenylaryl, substituted alkynyl, substituted aryl,  
 substituted alkylaryl, substituted cycloalkyl and substituted  
 alkylcycloalkyl and  $R_2$  and  $R_5$ , or  $R_5$  and  $R_6$  in combination,  
 are substituted cycloalkyl and substituted saturated  
 heterocyclyl groups.

9. The solid support of claim 5 wherein said insoluble substrate is selected from the group of hydroxyl resins consisting of Wang resin and Merrifield resin.
10. The solid support of claim 7 wherein said insoluble substrate is selected from the group of hydroxyl resins consisting of Rink resin Sieber resin and PAL resin.
11. The solid support of claim 7 as represented by the formula:



wherein P is a polymer backbone,  $R_6$  is a covalent bond; and  
 $R_3$  and  $R_4$  are hydrogen,  $R_1$  is hydrogen, substituted  
 alkylsilyl, substituted alkyl, substituted alkenyl;  $R_2$  and  $R_5$   
 are independently selected from a group consisting of  
 hydrogen, substituted amino, substituted hydroxyl,  
 substituted alkyl, substituted alkenyl, substituted  
 alkenylaryl, substituted alkynyl, substituted aryl,

- 10 substituted alkylaryl, substituted cycloalkyl and substituted alkylcycloalkyl and where  $R_1$  taken in combination with either of  $R_2$  and  $R_5$  are substituted cycloalkyl and substituted saturated heterocyclyl groups.
12. The solid support of claim 11 wherein said polymer backbone is selected from the group of amino resins consisting of Rink resin, PAL resin and Sieber resin.
13. A method for the preparation of 4-and 5-amino- $\alpha,\beta$ -unsaturated ester solid support templates comprising the steps of:
- 5 a. hydrolyzing a halogen substituted alkene ester containing between 4 and 5 carbon atoms to form a free carboxylic acid;
- b. coupling said free halogen substituted carboxylic acid to a polymer backbone through a linker to form a halogenated unsaturated ester solid support template;
- 10 and
- c. replacing said halogen with an amino moiety.
14. The method of claim 13 wherein said halogen of said halogen substituted alkene ester is first replaced by a protected amino group and then hydrolyzed to form said free carboxylic acid prior to coupling to said polymer backbone.
15. A method for the preparation of 4-and 5-amino- $\alpha,\beta$ -unsaturated ester solid support templates comprising the steps of
- a. converting an  $\alpha$ - or  $\beta$ -amino acid derivative to its

- 5 corresponding carbonyl derivative;
- b. reacting said derivative with an ylid containing to  
form 4-and 5-amino- $\alpha,\beta$ -unsaturated ester; and
- c. hydrolyzing said 4-and 5-amino- $\alpha,\beta$ -unsaturated  
10 ester to form a free carboxylic acid prior to coupling to  
said polymer backbone, and
- d. coupling said free acid to a polymer backbone  
through a linker.

16. A method for the preparation of 4-and 5-amino- $\alpha,\beta$ -  
unsaturated ester solid support templates comprising the  
steps of:
- a. preparing a ylid on a polymer support through a  
5 linker;
- b. coupling an N-protected  $\alpha$  or  $\beta$  amino carbonyl  
compound to said ylid under basic conditions, said  
amino compound being selected from the group  
consisting of an amino-ketone or an amino-aldehyde  
thereby to form a solid support comprising a template  
selected from the group consisting of 4- and 5- amino-  
10  $\alpha,\beta$ -unsaturated ester.
17. A polymer bound heterocycle scaffold prepared with the solid  
support template made by the method of claims 13-16.

18. The polymer bound heterocycle scaffold of claim 17 wherein  
said heterocycle scaffold is selected from the group  
consisting of to piperazinone, piperazine, morpholine,  
morpholinone, benzodiazepine, benzodiazepinone,  
hydantoin, thiohydantoin, imidazole, imidazolidone, cyclic  
5 urea, cyclic thiourea, thiazole, oxazole, pyrazole, lactone,  
lactam, tetrahydroquinoxaline.
19. An array of polymer bound heterocycle compounds prepared  
using the solid support template made by the method of  
10 claims 13-16.

## INTERNATIONAL SEARCH REPORT

Intern application No.

PCT/US01/41615

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : 427/215, 216, 220; 428/403, 404, 406, 407; 525/54.21, 54.22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 427/215, 216, 220; 428/403, 404, 406, 407; 525/54.21, 54.22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,324,776 A (BUYSCH et al) 28 June 1994, see entire document.	1-19
A	US 6,117,940 A (MJALLI) 12 September 2000, see entire document.	1-19

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"A" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 SEPTEMBER 2001

Date of mailing of the international search report

16 NOV 2001

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# INTERNATIONAL SEARCH REPORT

Inter: of application No.

PCT/US01/41615

## A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

B05D 7/00; B32B 15/02, 17/02, 19/00, 21/02, 23/02, 27/02; C08G 18/00, 63/48, 63/91